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**BIOMEDICAL ENGINEERING AND INSTRUMENTATION BRANCH
DIVISION OF RESEARCH SERVICES
NATIONAL INSTITUTES OF HEALTH**

ANNUAL REPORT FY 1985

Dr. Murray Eden, Chief



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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 RS 10001-17 BEI
PERIOD COVERED October 1, 1984 to September 30, 1985		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Pharmacokinetics		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) R.L. Dedrick Chief, ChES BEIB, DRS		
Others: F. Farris North Dakota State University BEIB, DRS R. J. Lutz Chemical Engineer BEIB, DRS F. King Chemical Engineer BEIB, DRS P. F. Morrison Physical Scientist BEIB, DRS		
COOPERATING UNITS (if any) CPB, NCI (J.M. Collins); LMCB-NCI (C.L. Litterst); DR-CC (J.L. Doppman); CP-CC (G. Hook); NTP-NIEHS (H.B. Matthews); SNB-NINCDS (E.H. Oldfield, C. Clark); University of Maryland (M.Egorin; M.F. Flessner).		
LAB/BRANCH Biomedical Engineering and Instrumentation		
SECTION Chemical Engineering Section		
INSTITUTE AND LOCATION DRS, National Institutes of Health, Bethesda, MD 20205		
TOTAL MAN-YEARS: 1.0	PROFESSIONAL: 1.0	OTHER:
CHECK APPROPRIATE BOX(ES) ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither ☐ (a1) Minors ☐ (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) Pharmacokinetic models are developed for the distribution and disposition of drugs, environmental contaminants, and endogenous metabolites in animals and man. They provide a plausible set of equations that can be used to extrapolate data from animals to man and thereby improve chemotherapy and risk assessment. Emphasis has been placed on regional drug administration, and this has led to the development of spatially distributed models of drug transport in tissue. These analyses have provided considerable insight into the penetration depths of drugs administered intraperitoneally or by infusion into the brain. The penetration of cis-dichlorodiammineplatinum (II) (DDP) into peritoneal and subperitoneal tissue is being examined experimentally with an electron probe and the results compared with a reaction-diffusion equation of the process. A lumped model of DDP pharmacokinetics has been developed to include both metabolism to a mobile species and covalent binding to macromolecules. Pharmacokinetic theory which was developed for intra-arterial drug administration combined with extracorporeal treatment of venous drainage had been validated in the clinic. Systemic exposure to DDP has been reduced by 49-74% by hemodialysis of jugular venous drainage during intracarotid artery infusion for the treatment of malignant glioma. Preliminary results have shown the feasibility of documenting appropriate vascular drainage with indocyanine green.		

OBJECTIVES: Improve and extend mathematical models for the distribution and disposition of drugs, environmental contaminants, and endogenous metabolites in animals and man to:

- (1) Account for species differences in drug distribution.
- (2) Provide a rational basis for extrapolating toxicity from animals to man.
- (3) In conjunction with pharmacodynamics, provide a basis for optimizing cancer chemotherapy.
- (4) Enable rational transfer of in vitro thermodynamic and kinetic data to in vivo cases.
- (5) Predict effective dose schedules of anticancer drugs in individual patients with particular emphasis on regional drug delivery.

METHODS EMPLOYED: Mathematical models are developed from physicochemical, physiological, and anatomical information and the principles of chemical reaction engineering. Resulting ordinary or partial differential equations are solved analytically or numerically and compared with experimental data. Uncertainties are clarified by additional experiments and model modification.

MAJOR FINDINGS: (1) A physiologic model has been developed to describe the pharmacokinetics of cis-dichlorodiammineplatinum (II) (DDP) in the tumored rat. The rat model has been used to perform a pharmacokinetic analysis for the rabbit, dog and human. The results are compared to the rat. DDP binds irreversibly to low MW nucleophiles and macromolecules to form mobile and fixed metabolites at rates which are tissue specific. The rate constant for the formation of fixed metabolite in plasma, determined by *in vitro* incubation, ranged from 0.004 - 0.008 min⁻¹. Filterable platinum is eliminated at rates approximating GFR in all species. Biliary excretion accounts for 1-4% of dose and was neglected. The tissue-specific DDP-to-protein binding rates were estimated from the ratio of tissue concentration to plasma concentration at long times and were scaled relative to the plasma binding rate. The relative binding rates were in the order kidney/skin/liver/gut/muscle for the rat and dog. The rates for the rabbit were similar except that the skin and liver were reversed. Tissue-specific binding rates were generally similar among species. The rates of release of Pt from macromolecules are consistent with protein turnover rates. The turnover rate remains constant or decreases with increasing body weight for all species. Human pharmacokinetic behavior was predicted by estimating human parameters by extrapolation of the animal data. The simulations in humans were compared to experimental plasma concentration and urine excretion profiles from a number of published studies.

(2) X-ray microanalysis has been investigated as a means of measuring cisplatin concentration profiles in tissues following intraperitoneal infusion. Doses of cisplatin in the range of 25-35 mg/kg have been given to rats in 35 ml of physiological saline. Tissues from the anterior abdominal wall have been most thoroughly investigated, revealing a concentration of Pt in the first 20 microns of the peritoneal side. Profiles in other tissues and

in abdominal wall regions outside of the 20-micron band have not yet proven obtainable. Spectroscopic parameters required for analysis have been identified. These include use of the Pt M alpha line and a high electron voltage (20 kv or higher) since the peak-to-background ratio remains relatively constant above 8 kv. The Pt M alpha line lies on the shoulder of a phosphorous peak but separates from it sufficiently well to allow analysis. Sulfur was measured in the 20 micron Pt band and in both the extra and intracellular regions of the muscle tissue, and very similar levels were obtained in all regions. This is consistent with similar concentrations of sulfate-ion sulfur in the intracellular medium and glycosaminoglycan sulfate sulfur in the connective tissue (extracellular space), particularly in view of the sulfate ion's ability to diffuse during section drying. Thus the high protein sulfur potentially responsible for Pt binding in the 20 micron peritoneal band cannot be singled out by the electron probe for direct measurement.

Sensitivity of the probe to Pt has been estimated as 40 ppm (dry fraction basis) provided tissue sections are placed on thin polymeric films. Present efforts are aimed at determining whether the > 40 ppm bulk tissue concentrations estimated from intraperitoneal pharmacokinetic data in dogs can be observed by the probe.

(3) The pharmacokinetic advantage of intra-arterial drug administration can be increased if blood from the infused region is passed through an extracorporeal device which removes drug before the blood is returned to the body. Four patients with malignant gliomas received infusions of DDP into the internal carotid artery at a dose of 100 mg/m² infused at 15 ml/min for 1 hour while blood from the ipsilateral jugular bulb was dialyzed through two hollow fiber hemodialyzers in series. Plasma samples were obtained at frequent intervals from the dialyzer inflow, dialyzer outflow and right atrium for measurement of total and filterable platinum. In addition, the dialysate outflow was assayed to confirm the material balance. The reduction in systemic exposure could be calculated by four independent means: (1) reduction in the area under the free platinum curve compared with i.a. infusion without dialysis; (2) reduction in platinum bound to plasma proteins compared with simple i.a. infusion; (3) amount of platinum removed from the blood; and (4) amount of platinum appearing in the dialysate. By these measures, hemodialysis reduced systemic exposure by 49 to 74%. The estimated pharmacokinetic advantage was increased from a range of 3.5-4.7 associated with arterial infusion to a range of 5.2-8.1 with arterial infusion and hemodialysis of jugular venous blood, an average increase of 77%. Doses of 200 mg/m² combined with hemodialysis are currently being studied in the clinic combined with validation of appropriate vascular drainage by indocyanine green.

SIGNIFICANCE: Drugs and other chemicals are tested for effect in animals, with the aim of extrapolating results to man. At issue are both the risk associated with environmental contaminants and optimization of therapy.

PROPOSED COURSE: Continued pharmacokinetic modeling with consideration of pharmacodynamic and cytokinetic events and drug interactions. Continued clinical emphasis through support of regional procedures and other measures to overcome drug resistance. Research designed to investigate distribution and metabolism of environmental contaminants and on methods for incorporating

pharmacokinetics in models of risk assessment. Investigation of use in in vitro assays of chemical metabolism in conjunction with pharmacokinetic models for quantitative prediction of metabolism in vivo. Extension of distributed models for description of drug movement through tissue.

PUBLICATIONS

Lutz R.J., Dedrick, R.L., Tuey, D., Sipes, I.G. Anderson, M.W., and Matthews, H.B.: Comparison of the pharmacokinetics of several polychlorinated biphenyls in mouse, rat, dog and monkey by means of a physiological pharmacokinetic model. Drug Metab. Disp. 12: 527-535, 1984.

Dedrick, R.L., Flessner, M.F., Collins, J.M., and Shultz, J.S.: A distributed model of peritoneal transport. Proc. III. Int. Symp. Peritoneal Dialysis (in press).

Flessner, M.F., Dedrick, R.L., Fenstermacher, J.D., Blasberg, R.G., and Sieber, S.: Peritoneal absorption of macromolecules. Proc. III. Int. Symp. Peritoneal Dialysis (in press).

Dedrick, R.L.: Application of model systems in pharmacokinetics. In Banbury Report 19: Risk Quantitation and Regulatory Policy, Cold Spring Harbor Laboratory, NY 1985, pp. 187-196.

Dedrick, R.L.: Application of model systems in pharmacokinetics. In Silvers A., and Newell, G.W. (Eds.): New Directions in the Extrapolation of Animal Data to Man, Vol. 2. Toxicokinetics. Palo Alto, CA, Electric Power Research Institute, (in press).

Oldfield, E.H., Dedrick, R.L., Yeager, R.L., Clark, W.C., DeVroom, H.L., Chatterji, D.C., and Doppman J.L.: Reduced systemic drug exposure by combining intraarterial chemotherapy with hemoperfusion of regional venous drainage, J. Neurosurg. (in press).

Farris, F.F., King, F.G., Dedrick, R.L., and Litterst, C.L.: Physiological model for the pharmacokinetics of cis-dichlorodiammineplatinum (II) (DDP) in the tumored rat, J. Pharmacokinet. Biopharm. 13: 13-39, 1985.

Flessner, M.F., Dedrick, R.L., and Schultz, J.S.: Exchange of macromolecules between peritoneal cavity and plasma, Am. J. Physiol. 248: H15-H25, 1985.

Flessner, M.F., Fenstermacher, J.D., Blasberg, R.G., and Dedrick, R.L.: Peritoneal absorption of macromolecules studied by quantitative autoradiography, Am. J. Physiol 248: H26-H32, 1985.

Oldfield, E.H., Dedrick, R.L., Chatterji, D.C., Yeager, R.L., Girton, M.E., Kornblith, P.L., and Doppman, J.L.: Arterial drug infusion with extracorporeal removal. II. Internal carotid carmustine in the rhesus monkey, Cancer Treatment Rep. 69: 293-303, 1985.

Clark, W.C., Daniels, C.E., Dedrick, R.L., Girton, M.F., Doppman, J.L., and Oldfield, E.H.: Aspiration of blood from the jugular vein during intracarotid drug infusion in monkeys, J. Neurosurg. 62: 576-579, 1985.

Z01 RS 10001-17 BEI

Flessner, M.F., Dedrick, R.L., and Schultz, J.S.: A distributed model of peritoneal-plasma transport: analysis of experimental data in the rat, Am. J. Physiol. 248: F413-F424, 1985.

Flessner, M.F., Fenstermacher, J.D., Dedrick, R.L., and Blasberg, R.G.: A distributed model of peritoneal-plasma transport: tissue concentration gradients, Am. J. Physiol. 248: F425-F435, 1985.

Lutz, R.J., and Dedrick, R.L.: Physiological pharmacokinetics: relevance to human risk assessment, In Li, A.P. (Ed.): Toxicity Testing - New Approaches & Applications in Human Risk Assessment, New York, Raven, 1985, pp. 129-149.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01-RS-10002-20-BE I
PERIOD COVERED Oct.1, 1984 to Sept. 1985		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Implant Device Development		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) John W. Boretos, Physical Scientist, BEIB, DRS John Doppmann, M.D. Radiologist CR, CC, NIH Edward Oldfield, M.D. Neurosurgeon NINCDS, NIH F.T. Hambrecht, M.D. Health Science Adm. NINCDS, NIH		
COOPERATING UNITS (if any) CR, CC, NIH; NS, NINCDS, NIH; FNP, NINCDS, NIH; BEIB, DRS, NIH.		
LAB/BRANCH Biomedical Engineering and Instrumentation		
SECTION Chemical Engineering		
INSTITUTE AND LOCATION DRS, NIH, Bethesda, MD. 20205		
TOTAL MAN-YEARS: 1.0	PROFESSIONAL: 0.7	OTHER: 0.3
CHECK APPROPRIATE BOX(ES) ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither ☐ (a1) Minors ☐ (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) The purpose of this project is to elucidate the interaction of biomaterials used for specific implants with the physiological environment and to explore specially prepared biomaterials and design features with respect to their suitability and performance in a variety of contexts. Polyurethanes are an important class of elastomers for use in catheters, heart assist pumps, electrode insulation and similar implant applications. Variations in the basic chemical structure of these polymers as well as physically induced stress can severely reduce their effectiveness for long-term use as a surgical device. Previous studies undertaken by this project have shown a relationship between the molecular chain structure in resisting hydrolytic forces. Recent evidence suggests that physical forces such as stress induced during fabrication can promote a form of stress corrosion. <u>In vitro</u> test data and SEM photomicrographs of surgical explants of various polyurethane classes show that premature failure is often the result of a combination of forces acting on the polymer at stress risers. A strong correlation exists between these <u>in vitro</u> and <u>in vivo</u> observations over short and long term periods of study.		

Z01 RS 10002-20 BEI

OBJECTIVES: Elucidate the interaction of polymers, metals, and ceramics used for specific implants with the physiological environment; explore specially prepared polymers, their properties and design features with the physiological environment in a variety of contexts.

METHODS EMPLOYED: Basic composition of biomaterials is carefully controlled, and modifications are employed to enhance acceptability by the living system. After removal, implants are examined for lipid absorption, protein and/or calcium deposition, changes of surface-free energy and alteration of physical properties. Observation techniques include SEM, infrared spectroscopy, contact angle measurements, energy dispersive x-ray analysis, and atomic absorption spectroscopy. Electronic implants are examined periodically in vivo for changes in threshold levels, corrosion, and tissue activity. In vitro studies of the aforementioned are designed to accelerate fatigue testing and methods for improvement of components undergoing stress.

MAJOR FINDINGS: Polyurethanes are a complex and varied class of polymers whose full potential for medical use has not been achieved. Characterization of its behavior under conditions of use is necessary to project its safety and efficiency as a surgical implant. Variations in the basic chemical structure of these polymers as well as physically induced stress can severely reduce their usefulness. Previous studies undertaken by this project have shown a direct relationship between the molecular structure of the polymeric chain and its ability to resist hydrolysis.

SIGNIFICANCE: Physiologically compatible polymers with enduring strength are needed for surgical implants, indwelling catheters, and subcutaneous uses.

PROPOSED COURSE: Extend experimental studies to further characterize the surface and bulk properties of biomaterials and, more specifically, to determine their interactions with blood and subcutaneous tissue to facilitate development of better surgical implants.

PUBLICATIONS

Boretos, J.W.: Correlation of long-term data for segmented polyurethanes. In Planck, H., Egbers, G., and Syre, I. (Eds.): Polyurethanes in Medical Techniques. Amsterdam, Elsevier, 1984, pp. 135-142.

Boretos, J.W.: Cellular polymers for medical use: the vital role of porosity and permeability. Cellular Polymers 3 (5): 345-358, 1984.

Boretos, J.W., Girton, M.E., and Doppman, J.L.: Polyurethane radiopaque marker for indwelling devices. J. Biomed. Mater. Res. (in press).

Boretos, J.W.: Ceramics in clinical care (abstract). Extended Abstracts, American Ceramic Society, 89th Annual Meeting, Cincinnati, Ohio, May 5-9, 1985, p. 285.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 RS 10015-10 BEI
PERIOD COVERED October 1, 1984 to September 30, 1985		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Development of Toposcopic Catheter for Clinical Vascular Use		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) PI: D.R. Shook, Biomedical Engineer, BEIB, DRS J.L. Doppman, Chief, DRD, CC E.H. Oldfield, Senior Staff Neurosurgeon, SNB, NINCDS		
COOPERATING UNITS (if any) Diagnostic Radiology, CC (J.L. Doppman); Surgical Neurology, NINCDS (E.H. Oldfield)		
LAB/BRANCH Biomedical Engineering and Instrumentation Branch		
SECTION Mechanical Engineering Section,		
INSTITUTE AND LOCATION DRS, National Institutes of Health, Bethesda, MD 20205		
TOTAL MAN-YEARS: 0.8	PROFESSIONAL: 0.3	OTHER: 0.5
CHECK APPROPRIATE BOX(ES) ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither ☐ (a1) Minors ☐ (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) Toposcopy has been shown to be a reliable clinical means to catheterize long, small diameter, and highly tortuous blood vessels, inaccessible by previous techniques. A toposcopic element everts from the tip of a conventional catheter. This extremely flexible polyurethane element has been fabricated in 3, 4 and 5 French sizes mated with 5, 6 and 7 French catheters, respectively, and is capable of eversion lengths in excess of 40 cm. The toposcopic catheter has been applied clinically for the local delivery of chemotherapy to brain tumors. Treatment is provided by positioning the conventional catheter in the internal carotid artery from a femoral entry; everting the toposcopic element through the carotid sinus, beyond the ophthalmic artery to avert retinal toxicity; and perfusing the tumor through the middle and/or anterior cerebral arteries. Note that a conventional catheter cannot safely negotiate the tortuosity of the carotid sinus. The catheter has been extensively used clinically in its present prototype form, and production techniques for its fabrication are being transferred to private industry to provide for a ready source of catheters for future studies.		

Z01 RS 10015-10 BEI

OBJECTIVES: Develop techniques for selective toposcopic catheterization of small, tortuous blood vessels and optimize apparatus for varied diagnostic and therapeutic applications.

MAJOR FINDINGS: Eversion, infusion, and retraction of the catheter have occurred without incident in over thirty clinical chemotherapeutic treatments. Implementation of existing techniques to direct catheter eversion is required in some difficult anatomical situations. Continued follow-up of these patients has suggested that treatments at low infusion rates may be hampered by inadequate infusate/blood mixing. Recent literature reports indicate that this problem is, to a great extent, independent of the catheter and more a consequence of the minute flow rates involved (1 ml/min). Therefore, independent studies have been initiated to fully characterize the problem and to evaluate the effectiveness of pulsed intra-arterial infusion as a clinical solution.

SIGNIFICANCE: By atraumatically negotiating small, highly tortuous blood vessels, the catheter reaches heretofore inaccessible regions for both diagnostic and therapeutic application. Thus, routine fluoroscopic examinations are readily augmented by selective treatment modalities for tumors, aneurysms, arterio-venous malformations, and other lesions which previously required major surgical interventions.

PROPOSED COURSE: Optimize catheter system for diverse clinical applications. Transfer production technology to private industry for ready source of catheters. Investigate significance of infusate/blood mixing efficiency at tip of catheter. Develop wire guiding, remote steering and arterial dilatation methods. Develop related devices and explore additional uses for the catheter.

Related Project Number:

Z01-RS-10001-15 BEIB

Z01-RS-10 -01 BEIB (GI use)

Z01-RS-10 -01 BEIB (Polymer Processing)

Z01-RS-10 -01 BEIB (Pulsed Intra-arterial Infusions)

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 RS 10034-08 BEI
PERIOD COVERED October 1, 1984 to September 30, 1985		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Three-Dimensional Histological Reconstruction		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) S.B. Leighton, Mechanical Engineer, BEIB, DRS A.M. Kuzirian, Neuroanatomist, LB, NINCDS		
COOPERATING UNITS (if any) LB NINCDS		
LAB/BRANCH Biomedical Engineering and Instrumentation		
SECTION Mechanical Engineering Section		
INSTITUTE AND LOCATION National Institutes of Health, Bethesda, MD 20205		
TOTAL MAN-YEARS: .3	PROFESSIONAL: .3	OTHER:
CHECK APPROPRIATE BOX(ES) ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither ☐ (a1) Minors ☐ (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) A semi-automatic system for acquiring <u>three-dimensional structural</u> information about <u>histological</u> material is being developed. The system should have significant speed and reliability advantages over present techniques using serial sections, although resolution may be limited. In brief, an embedded tissue block will be fixed relative to a <u>scanning electron microscope</u> imaging system, the surface of the block will be imaged and the image stored, and successive slices will be removed by a built-in <u>microtome</u>. Handling and registration of thin sections will thus be eliminated. Human and computer pattern recognition will transform the resulting set of images into a three-dimensional reconstruction. Oxygen plasma etching has been found to give sufficient topographic relief that the resolution of the images is now limited by the SEM and not by the preparation technique. The images of <u>Hermisenda Crassicornis</u> obtained by this technique correlate well with TEM images of the same tissue, indicating that the lack of artifact is adequate for the contemplated studies.		

Z01 RS 10034-08 BEI

OBJECTIVES: (1) To facilitate making schematic diagrams of neural networks. (2) To facilitate developmental studies of small organs and organisms. (3) To do three-dimensional reconstruction of biological structures.

METHODS EMPLOYED: A miniature microtome has been built to function within the vacuum chamber of a scanning electron microscope. The microtome has cut sections as thin as 0.5 microns. Epoxy has been tried as a embedding medium, and oxygen plasma as an etching means.

MAJOR FINDINGS: The microtome knife and specimen feed mechanisms have been rebuilt for all electronic operation to facilitate interfacing with a computer and with a new SEM, and to remove the risk of fluid leaks into the SEM. The new specimen drive is capable of 5000 Angstrom section thickness. A miniature gold gun (2.5 x .6 cm) has been successfully tested. This in situ evaporation source can apply a 200 Angstrom gold layer in 30 seconds and can apply approximately 200 layers before requiring refilling. Total time per image (cut, etch, coat, view) is expected to be less than 7 minutes. The system has been integrated with a new SEM in LB, NINCDS.

SIGNIFICANCE: Neuroanatomists may be able to trace significant neural nets with sufficient ease to allow a statistically significant number of samples. Other biological studies may be materially aided.

PROPOSED COURSE: Parameters such as etching time and intensity will be optimized. We will attempt more routine use of the instrument, and will try an actual reconstruction of a small neural network in Hermisenda Crassicornis. X-ray image analysis will also be tried. Computer control will be planned.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 RS 10039-08 BEI
PERIOD COVERED October 1, 1984 to September 30, 1985		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Biophysical Instrumentation and Methodology		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) Marc S. Lewis, Research Chemist, BEIB/DRS Other: Thomas R. Clem, Electronics Engineer BEIB/DRS		
COOPERATING UNITS (if any)		
LAB/BRANCH Biomedical Engineering and Instrumentation		
SECTION Analytical Methods		
INSTITUTE AND LOCATION DRS, National Institutes of Health, MD 20205		
TOTAL MAN-YEARS: 0.1	PROFESSIONAL: 0.1	OTHER:
CHECK APPROPRIATE BOX(ES) ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither ☐ (a1) Minors ☐ (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) The project is designed to develop new instrumentation and methodology or improve existing instrumentation and methodology for characterization of biological macromolecules and for studying their interactions. Analytical ultracentrifugation, the techniques ancillary to it, and methods of data analysis using mathematical modeling appropriate for these techniques are the major areas of interest. A microprocessor controlled system for the direct acquisition of data from the photomultiplier tube of the ultraviolet absorption scanner of the ultracentrifuge and for the control of that acquisition has been developed. The software requisite for making this system operational is presently in a developmental stage. When complete, this system will permit direct acquisition of data in digital form while the ultracentrifuge is operating and then permit preliminary data processing followed by transmission of the data to the DEC-10 computer for detailed analysis. A study has been initiated on the possibility of development of new optical data acquisition systems for the conversion of current preparative ultracentrifuges into analytical ultracentrifuges with superior capabilities as analytical instruments at a fraction of the cost of the current instruments. Preliminary designs for such systems have been developed. MLAB, operating on the DEC-10 computer, has been used for mathematical modeling studies for the analysis of various types of protein interactions. These studies have been applied to ultracentrifugal studies of binding and of protein self-association. Such studies are described in the project report entitled Physical Chemistry of Biological Macromolecules.		

OBJECTIVES: To develop data acquisition systems for analytical ultracentrifuges and for ancillary equipment such as plate or film readers and densimeters, to develop appropriate software to use with the acquisition systems, to develop new instrumentation for the conversion of preparative ultracentrifuges into analytical ultracentrifuges and to study means of utilizing MLAB more effectively for the analysis of ultracentrifuge data by mathematical modeling techniques.

METHODS EMPLOYED: A microprocessor controlled instrument has been developed for the direct acquisition and storage of data from the photomultiplier tube of the ultraviolet absorption optical scanning system of the analytical ultracentrifuge. This instrument is coupled to a Columbia Data Systems desk-top minicomputer which provides (1) temporary data storage in the computer as well as permanent storage on floppy discs; (2) preliminary processing, graphic display and editing of the data; and (3) communication with the DEC-10 computer permitting transfer of the data to be processed to the DEC-10, control of data analysis using the MLAB system on the DEC-10 and finally, the transfer of the results of these analyses back to the laboratory. Software is being developed for optimizing the data acquisition for different modes of acquisition and for data editing prior to transmission to the DEC-10. The prospect that manufacturer's support for the current analytical ultracentrifuge will become more limited in future years has stimulated interest in the development of new optical systems with data acquisition systems for converting the present excellent preparative ultracentrifuges into analytical instruments. Preliminary designs for such systems have been developed.

MAJOR FINDINGS: Systems for the direct acquisition of data from the analytical ultracentrifuge have been demonstrated to have significant advantages in speed and accuracy when compared to the manual digitization of analog data and the manual entering of this data in the computer for analysis. Programs are being developed for the reduction of data acquired in different acquisition modes and for editing it prior to transmission to the DEC-10 computer for analysis. Improvement in the methods for the analysis of interacting systems of macromolecules by mathematical modeling utilizing MLAB on the DEC-10 computer have been continued. Systems of a variety of possible models of protein-protein interactions have been developed, including systems where binding is complicated by self-association of one or more of the components involved. The method of writing mathematical models where the physical properties of the system being studied are incorporated as implicit constraints on the model has been extended to more complex systems. This avoids the needs of applying external constraints to make the fitting parameters physically meaningful and also results in more efficient computation and more meaningful results. This method has been applied to work described in the annual report entitled Physical Chemistry of Biological Macromolecules. Preliminary studies indicate that it appears possible to develop very compact optical systems which will fit entirely within the vacuum chamber of a preparative ultracentrifuge, be easily removable to permit the normal preparative use of the instrument, and yet be capable of offering better precision than the current analytical ultracentrifuge.

SIGNIFICANCE: Since data acquisition has been the major limiting factor in terms of the qualitative and quantitative aspects of ultracentrifugal research, it is expected that the continuing development of data acquisition systems as described above will significantly facilitate such research. The

improved methods of data analysis by mathematical modeling also contribute significantly to the quality and the time and cost effectiveness of this research. The development of a new analytical ultracentrifuge will greatly facilitate such studies and will free the investigator from the constraints of obsolescent instrumentation.

PROPOSED COURSE: Continue the developments outlined above.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 RS 10043-08 HEI
PERIOD COVERED October 1, 1984 to September 30, 1985		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Fiber Optic Probes		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) John I. Peterson, Chemist, BEIB/DRS Stephen E. Epstein, Chief, H IR CB		
COOPERATING UNITS (# any) H IR CB H IR OD		
LAB/BRANCH Biomedical Engineering and Instrumentation		
SECTION Chemical Engineering Section		
INSTITUTE AND LOCATION DRS, National Institutes of Health, Bethesda, MD 20205		
TOTAL MAN-YEARS: .8	PROFESSIONAL: .8	OTHER:
CHECK APPROPRIATE BOX(ES) ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither ☐ (a1) Minors ☐ (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) A suitable device is needed for the direct measurement of oxygen partial pressure (PO_2) in blood and tissue for both clinical and research applications. Methods currently available for measuring PO_2 lack convenience, reliability, speed, and relevance to many situations of interest. Efforts to develop electrical sensors have not been successful. It is desirable to have a very small PO_2 sensor which can be inserted into a blood vessel or tissue with little disturbance, and which will provide instantaneous and current PO_2 monitoring for either short or extended periods of time. A fiber optic sensor is ideal for this application, with the advantage, for physiological use, of very small size and flexibility, safety, and low cost. A PO_2 sensor has been developed, based upon the principle of fluorescence quenching by oxygen. The feasibility of the sensor and its satisfactory performance has been demonstrated in <u>in vitro</u> and <u>in vivo</u> tests, in work in preceding years. In the past year, the development of the sensor as a needle probe was accomplished, and problems of storage life and stability were resolved. This provides a basis for practical application of the fiber optic PO_2 probe as a research tool.		

OBJECTIVES: Develop an oxygen sensor for implantation in the blood stream and tissues, to be used in studies of oxygen transport.

METHODS EMPLOYED: A fiber optic measurement of dye-indicator response to oxygen by fluorescence quenching.

SIGNIFICANCE: P02 measurements are fundamental to the understanding and control of oxygen transport in research and clinical investigations. Measurements on withdrawn blood samples lack convenience, reliability, and relevance to many situations of interest. Indirect estimation of P02 using spectrophotometric measurements of hemoglobin oxygenation and the concentration-pressure transfer function (blood oxygen saturation curve) is subject to many uncertain variables. Development of a fiber optic P02 probe represents a significant advance in the ability to directly and continuously measure blood and tissue oxygen. A satisfactory electrode for general use has never been developed, and the fiber optic approach offers some distinct advantages in small size, flexibility, and safety.

MAJOR FINDINGS AND PROPOSED COURSE: In the year past, the following goals were achieved:

1. A method of making the sensor in needle form was developed. This was one of the original objectives of the sensor development, to provide a tool for ischemia related studies, and to find whether direct P02 measurement is of value in preservation of heart tissue during surgery. The previously developed pH sensor was used similarly.
2. The instrument design and probe construction were changed to allow single fiber construction of the sensor. This provides simpler construction, smaller size, and better performance.
3. The problem of shelf life of the sensor was resolved, so that a sensor does not have to be made and used within a brief period of days.
4. The problem of sensitivity of the sensor to interference by volatile halogenated anesthetics was not solved. It is viewed that this is not a serious problem for research applications, and is a fundamental property of this type of sensor.

Work in the current year is directed toward evaluating the suitability of the sensor for various applications, and improving its stability.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 RS 10064-05 BEI
PERIOD COVERED October 1, 1984 to September 30, 1985		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Indirect Blood Pressure Measurements in Laboratory Animals Using Oscillometry		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) E.C. Walker, Mechanical Engineer, ACES, BEIB		
COOPERATING UNITS (if any) SLAMS OD NHLBI		
LAB/BRANCH Biomedical Engineering and Instrumentation		
SECTION Applied Clinical Engineering		
INSTITUTE AND LOCATION DRS, National Institutes of Health, Bethesda, MD 20205		
TOTAL MAN-YEARS: 0.25	PROFESSIONAL: 0.25	OTHER:
CHECK APPROPRIATE BOX(ES) ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither ☐ (a1) Minors ☐ (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) Currently there are no reliable <u>indirect methods</u> of measuring <u>blood pressure</u> in <u>dogs</u>. Traditional techniques, used in humans, are unsatisfactory primarily because they require the placement of a transducer over the artery being monitored. Because of the unreliability of traditional techniques we have been investigating a technique called <u>oscillometry</u>. Oscillometry is the method of measuring blood pressure by analyzing the <u>pulse pattern</u> of the <u>cuff pressure</u> <u>oscillations</u>. In practice, a cuff is placed around a limb and inflated to a pressure above systolic and then deflated slowly. While the cuff is being deflated the amplitude of oscillation in cuff pressure, produced by the arterial pulse beneath the cuff, is monitored. <u>Systolic</u> and <u>diastolic</u> transitions in the oscillometric waveform are then used to indicate the indirect systolic and diastolic pressures respectively.		

Z01 RS 10064-05 BEI

OBJECTIVES: The primary objective of this project is to develop an instrument to measure peripheral arterial blood pressure indirectly in laboratory animals. A further objective is to base the design of this instrument upon physiological principles underlying the measurement technique employed.

METHODS EMPLOYED: A model of the oscillometric process is currently being employed to develop and test an automated oscillometric instrument. The model consists of a simulated artery, cuff, sinusoidal pressure generator, and a Tektronix 4052 computer.

SIGNIFICANCE: Animal surgery labs and other laboratories or veterinarian offices could use an indirect device on a daily basis. For various laboratory studies monitoring blood pressure in awake animals is very desirable, particularly with protocols involving atherogenic diets, and drug therapy. Another area of application would be in screening animals for hypertension research. For surgical procedures, an indirect technique will allow blood pressure monitoring before and during induction of anesthesia.

MAJOR DEVELOPMENTS: In addition to having the capability of measuring the systolic and diastolic pressures, oscillometry is also used to measure the mean arterial pressure. In order to incorporate a mean arterial measurement we have studied the relationship of maximum cuff pressure oscillation to mean arterial pressure. Our studies have shown that under proper conditions maximum pressure oscillation can be used to measure mean arterial pressure. The studies have also shown that maximum cuff pressure oscillation correlates very well with the sum of diastolic pressure and arterial collapse pressure. Thus, although maximum cuff pressure oscillation can be used to measure MAP it appears to be an intrinsic measurement of the sum of diastolic pressure and the pressure required to collapse the artery at diastole.

We have developed our own blood pressure cuffs to suit the unique anatomy of the dog but they are also quite useful in humans. The cuffs are ultra light, very thin, washable, and strong. Additionally, the cuffs are adaptable to a variety of anatomical locations. An NIH patent of our design has been applied for.

Using the results of in vivo and in vitro studies an algorithm has been designed to measure systolic and diastolic pressures in the dog oscillometrically.

The algorithms employed in our technique, which are based upon physiological principles, are still under development. Although bench tests support the accuracy of our technique, the effects of animal noise artifact will have to be sufficiently rejected.

PROPOSED COURSE: Future efforts will be directed toward improving our computer algorithms. We will also evaluate commercially available instruments designed for human use.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 RS 10073-06 BEI
PERIOD COVERED October 1, 1984 to September 30, 1985		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Secondary Emission Mass Spectrometer		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) L. Kelner, Senior Staff Fellow, BEIB, DRS Others: M. Eden Chief BEIB, DRS T. Patel Chemist BEIB, DRS		
COOPERATING UNITS (if any) LCS, NIMH (S.P. Markey), LC, NHBLI (H. Fales), DCRT, DRS (R. Tate)		
LAB/BRANCH Biomedical Engineering and Instrumentation Branch		
SECTION Office of the Chief		
INSTITUTE AND LOCATION DRS, National Institutes of Health, Bethesda, MD 20205		
TOTAL MAN-YEARS: 3	PROFESSIONAL: 2.5	OTHER: 0.5
CHECK APPROPRIATE BOX(ES) ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither ☐ (a1) Minors ☐ (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) We have initiated a systematic study of the energetics of various organic ions in relation to the different experimental conditions ion SIMS and FAB analysis. Knowledge of the energy distribution (ED) of secondary organic ions helps us to understand the mechanism of organic sputtering and provides information for the optimization of liquid SIMS. Based on our previous data, we proposed that the primary mechanism responsible for the emission of secondary organic ions is linear cascade sputtering, as this process results in the production of ions with lower kinetic energy. A major accomplishment in this FY was development-in collaboration with Teknivent, Inc.- of a data system based on an IBM PC-XT (256K), which was designed to control the quadrupole mass spectrometer of the SEMS system, and to scan the energy of secondary ions to produce energy distributions $N(E)=f(E)$. The computer system was used to scan the main cylinder voltage (V_m) of the electrostatic energy analyzer (Bessel Box) as well as to control the tandem quadrupole mass spectrometer. The target bias (V_t) remained fixed during the energy scan, and the energy distribution was determined as a function of ion intensity versus (V_m-V_t). Complete spectra were stored for each step of the energy scan. We have studied the energy distribution of secondary organic ions of arginine as well as effects of various liquid matrices on this parameter. Matrices employed included glycerol, triethanolamine, triethylglycol, and polyethyleneglycols, as well as protonating systems such as trifluoromethanesulfonic acid (TFMSA) and tartaric acid (TA).		

MAJOR FINDINGS:

Major results of our experiments can be summarized as follows:

- 1) The position of the maximum of ED changes significantly with the addition of protonated systems to the matrix. For example, addition of various amounts of TFMSA shifts the maximum of ED to lower energies when glycerol is the matrix material. As a rule, addition of TA shifts the ED maximum to a higher energy.
- 2) ED of the sample (arginine) as well as of the matrix ions very often exhibit a complex structure (two peaks). This double peak structure of ED can be explained by assuming that secondary ions sputtering is not a purely surface phenomenon, but that it also involves considerable disturbance of the adjacent volume (in the tens of angstroms). So-called recoil ions can produce lower energy secondary ions, while ions sputtered from the surface are of higher energy. The two peak structure of the ED changes with the type of matrix, concentration of sample in the matrix, and "doping" with protonating agents, such as TFMSA.
- 3) Observed dependence of the ED structure on the energy of primary particles reinforces our hypothesis, that this "splitting" of the ED into two peaks is a result of a superposition of two processes, one of which involves the monolayer on the surface and the second of which involves the volume of the target.
- 4) An almost complete suppression of the glycerol matrix and enhancement of the sample molecular peak (m/z 175, arginine) was observed at certain concentrations of TFMSA in the glycerol matrix.
- 5) ED of matrix ions depended on the concentration of a sample added to the matrix.

This work will continue by expanding into the studies of ED for various amino acids as well as other biologically significant compounds. Results of our studies for arginine were presented at the Annual Conference on Mass Spectrometry and Allied Topics on May 27, 1985 in San Diego, California.

A development of the data system for SEMS will continue to enable us to perform imaging analysis of biological specimens using SEMS system. This work is planned in collaboration with Teknivent, Inc. (Peter Norberg).

We have completed the adaption of the ion trajectory modeling program SIMION to the NIH DEC-10 system. The preliminary manual developed is sufficient for NIH scientists to use SIMION on DEC-10 for educational and development purposes.

Z01 RS 10073-06 BEI

PUBLICATIONS

Kelner, L., Markey, S.P., Fales, H.M., and Lundquist, T.: Secondary emission mass spectrometer. Application and Evaluation. Int. J. Mass Spectrom. Ion Proc., 62: 237-251, 1984.

Kelner, L., Fales, H.M., and Markey, S.P.: Molecular microprobe. Proceedings, 32nd Annual Conference on Mass Spectrom. Allied Topics, May, 1984.

Kelner, L., and Patel, T.: Energy distribution of secondary organic ions: Part II: Matrix Effect. Proceedings, 33rd Annual Conf. Mass Spectrom., May, 1985.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 RS 10096-05 BEI
PERIOD COVERED October 1, 1984 to September 30, 1985		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Light Scattering Method for Evaluation of Platelets		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) R. F. Bonner Physicist BEIB DRS		
T.R. Clem S.B. Leighton J. Frattoni B. Poindexter P. Mintz	Elect. Engineer Mech. Engineer Dir. Blood Bank Products Branch Biologist Director	BEIB DRS BEIB DRS DBBP, CDB, FDA BBPB, DBBP, CDB, FDA Blood Bank, U. Virginia
COOPERATING UNITS (if any) Center for Drugs and Biologics, FDA Blood Bank, U. Virginia		
LAB/BRANCH Biomedical Engineering and Instrumentation Branch		
SECTION Electrical and Electronic Engineering		
INSTITUTE AND LOCATION DRS, National Institutes of Health, Bethesda, MD 20205		
TOTAL MAN-YEARS: 0.4	PROFESSIONAL: 0.4	OTHER:
CHECK APPROPRIATE BOX(ES) ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither ☐ (a1) Minors ☐ (a2) Interviews		
SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.) Assessment of the functional status of platelets for transfusion is confounded by the inherent complexity of the cell, as well as the intricate requirements of sample preparation. A correlation between discoid shape and the functional integrity of the platelet has been established. We have developed a complex automatic machine based on previous experiments with a simple prototype which measures the fraction of the platelets that are discoid and the optical (volume) concentration of unaggregated platelets in standard blood bank platelet concentrate units within their bags. The microprocessor-based instrument automatically determines the volume concentration of unaggregated platelets and the fraction that are fully viable (discoid) during a 3-minute measurement sequence following simple insertion of the blood storage bag in the instrument. This process is noninvasive (sterile) and nondestructive. Thus it allows frequent measurements on the platelets prior to transfusion in order to optimize the quality and quantity of transfused platelets given patients. It also allows accurate investigations for optimizing storage and preparation methods. The instrument has been intensively studied with respect to invasive measurements of concentration and morphology of platelets and has proved to be highly accurate. In order to test the clinical significance of these measurements, a clinical evaluation of the instrumentation has begun at the Blood Bank of the University of Virginia. Platelet reversible morphological changes in heating from 20 to 32°C have been discovered with the instrument and are being studied in order to better understand the relation between platelet in vitro and in vivo.		

Z01 RS 10096-05 BEI

OBJECTIVES: Develop an optical method to evaluate platelets in standard blood storage bags and design and construct a practical clinical instrument using this noninvasive optical method. Develop and test optimal methods for the routine use of this technology in blood banking and transfusion.

METHODS EMPLOYED: Measurement of a large number of platelet concentrates on a simple prototype optical instrument in parallel with biochemical and visual grading providing a basis for the evaluation of the light scattering method. Light scattering theory applied to this data base led to the understanding of effects of the platelet number density and fraction that are discoid. This theoretical understanding provided the basis for the design parameters of the automatic instrument as well as its ability to automatically convert the raw optical signals into the desired concentration and viability fraction. It allows the use of the instrument with all the different types of commercial blood storage bags.

MAJOR FINDINGS: The automatic instrument can be used routinely by relatively unskilled technicians to evaluate quickly, noninvasively and nondestructively the quality and quantity of platelets in any standard storage bag. In preliminary tests the accuracy appears to be as good or better than that of the present invasive measurements not routinely allowed for a product that is transfused.

A newly developed multiple scattering theory very accurately predicts the optical scattering effects, which suggests further application to many type of concentrated cell suspensions.

SIGNIFICANCE: This method and instrument allow for the first time the optimal utilization of the blood bank product (platelet concentrate) for transfusion. It allows continuous quality control of the preparation and storage of the platelet concentrates at blood banks and hospitals. It may prove to be very useful in assessing new methods of preparing and storing the blood product for transfusion.

PUBLICATIONS

Bonner, R.F.: Noninvasive Optical Assessment of Platelet Viability. U.S. Patent #4,522,494, 1985.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 RS-10097-05
PERIOD COVERED October 1, 1984 to September 30, 1985		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Studies in Cardiovascular Dynamics		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) R.S. Chadwick, Biomedical Engineer, BEIB, DRS C. Oddou, Professor, University of Paris P. Brun, Senior Researcher, INSERM U. 138 B. Levy, Senior Researcher, INSERM U. 141 P. Peronneau, Chief, INSERM U. 256		
COOPERATING UNITS (if any) INSERM U.138 U.141 U.256 University of Paris XII, Laboratory of Physical Mechanics		
LAB/BRANCH Biomedical Engineering and Instrumentation		
SECTION Mechanical Engineering Section		
INSTITUTE AND LOCATION DRS, National Institutes of Health, Bethesda, MD 20205		
TOTAL MAN-YEARS: .4	PROFESSIONAL: .4	OTHER:
CHECK APPROPRIATE BOX(ES) ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither ☐ (a1) Minors ☐ (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) Our existing model for myocardial and ventricular mechanics will be refined to include an isotropic component of elasticity, passive and active viscoelasticity, non-cylindrical geometry, pathological fiber organization, and myocardial blood flow. The model will be used in conjunction with ultrasonic kinematic data to determine performance parameters. The physiological relationships between phasic coronary arterial and venous pressure and blood flow, aortic input impedance and ventricular dimensions will be determined. A mathematical and physical model of myocardial blood flow will be developed incorporating vessel collapse. Experimental techniques will be developed to measure vascular distensibility in man. RF backscatter from the myocardium will be investigated both experimentally and mathematically with the idea of determining the stress field. Theoretical models of wave propagation in arteries and aortic input impedance will be checked with experimental data.		

201 RS 10097-05 BEI

OBJECTIVES: To provide a framework for determining ventricular function, both at the fiber level and for the entire structure; to relate the relationship between coronary pressure and flow to the poro-elastic rheology of the myocardium; to provide a framework for evaluating those aspects of cardiovascular function that depend on the filling of, and ejection from the left ventricle; to develop new non-invasive measurement techniques for cardiovascular research.

METHODS EMPLOYED: An interdisciplinary approach will be utilized involving clinical ultrasound data, hemodynamic measurements on animals, physical models, and mathematical models.

SIGNIFICANCE: This research program with its interdisciplinary approach has the potential to increase fundamental knowledge in cardiovascular physiology.

PROPOSED COURSE: A Cardiovascular Dynamics Workshop is planned for September to discuss preliminary work. Two scientists will stay on for one month to work on a scattering theory for RF ultrasound backscatter from the myocardium, and to consider a theoretical model for ventricular filling abnormalities in cardiomyopathies.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 RS 10098-05 BEI																		
PERIOD COVERED October 1, 1984 to September 30, 1985																				
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Laser Instrumentation for Vitreous & Cardiovascular Microsurgery																				
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) R.F. Bonner Physicist BEIB DRS																				
<table style="width: 100%; border: none;"> <tr> <td style="width: 33%;">P.D. Smith Physicist BEIB, DRS</td> <td style="width: 33%;"></td> <td style="width: 33%;"></td> </tr> <tr> <td>M. Leon</td> <td>Sr. Investigator</td> <td>CB, NHLBI</td> </tr> <tr> <td>S. Epstein</td> <td>Chief</td> <td>CB, NHLBI</td> </tr> <tr> <td>D. Underhill</td> <td>Clinical Fellow</td> <td>SB, NHLBI</td> </tr> <tr> <td>R. Clark</td> <td>Chief</td> <td>SB, NHLBI</td> </tr> <tr> <td>R. Nossal</td> <td>Sr. Res. Physicist</td> <td>PSL, UCRT</td> </tr> </table>			P.D. Smith Physicist BEIB, DRS			M. Leon	Sr. Investigator	CB, NHLBI	S. Epstein	Chief	CB, NHLBI	D. Underhill	Clinical Fellow	SB, NHLBI	R. Clark	Chief	SB, NHLBI	R. Nossal	Sr. Res. Physicist	PSL, UCRT
P.D. Smith Physicist BEIB, DRS																				
M. Leon	Sr. Investigator	CB, NHLBI																		
S. Epstein	Chief	CB, NHLBI																		
D. Underhill	Clinical Fellow	SB, NHLBI																		
R. Clark	Chief	SB, NHLBI																		
R. Nossal	Sr. Res. Physicist	PSL, UCRT																		
COOPERATING UNITS (if any) Clinical Branch, NEI Cardiology Branch & Surgery Branch, NHLBI.																				
LAB/BRANCH Biomedical Engineering and Instrumentation																				
SECTION Electrical and Electronic Engineering																				
INSTITUTE AND LOCATION DRS, National Institutes of Health, Bethesda, MD 20205																				
TOTAL MAN-YEARS: 1.3	PROFESSIONAL: 1.3	OTHER:																		
CHECK APPROPRIATE BOX(ES) ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither ☐ (a1) Minors ☐ (a2) Interviews																				
SUMMARY OF WORK (Use standard unredacted type. Do not exceed the space provided.) This study entails the development and methodology of use of pulsed carbon dioxide laser systems, pulsed Nd:YAG laser coupled to a slit lamp, Q-switched Excimer lasers, and high-power CW Argon laser with fiber-optic delivery systems. For the CO₂ and Nd:YAG laser systems systematic studies of animal vitrectomies were performed in order to characterize laser pulse characteristics necessary to transect vitreal membranes. Additional studies of retinal damage as a function of pulse characteristics and distance of cutting site from the retina clarified the potential for use of these laser systems close to the retina. For all laser systems systematic studies of tissue damage on human coronary arteries was performed so as to determine their feasibility (and optimal system design) for laser angioplasty. The Argon laser/ fiber optic system was able to ablate artery wall and non-calcified plaque when probe was kept in contact with the bottom of the crater as it was formed. Argon laser systems could not ablate calcified lesions. High power nanosecond (or shorter) duration Nd:YAG laser pulses could easily remove noncalcified plaque but removed calcified plaque only very slowly. Additionally large fissures in the artery wall occurred, most likely the result of shock waves created by the transient absorption of the laser energy. Submillisecond CO₂ laser pulses ablated tissue with minimal thermal damage to surrounding tissue. Excimer laser pulses etched very clean craters in calcified as well as non-calcified plaque. Evaluation of prototype fiber-optic laser angioscopes in animals were carried out to evaluate this technology as an adjunct to surgery and as an aid in directing laser angioplasty. Human fiber-optic angioscopy during bypass surgery has been initiated.																				

OBJECTIVES: This study is designed to develop and test the efficacy and safety of laser systems for use in vitreous surgery. Studies of a large variety of laser systems with potential for laser angioplasty are being directed towards optimizing laser/fiber optic system for this experimental surgery and other cardiovascular microsurgery.

METHODS EMPLOYED: The safety and efficacy of the prototype units as well as an experimental prototype pulsed Nd:YAG system have been tested in rabbits and monkeys with vitreal membranes. Retinal damage mechanism were systematically examined in normal eyes as well. These systems, a high power Argon laser-fiber optic system, and infrared video thermography, tissue histology and tissue spectrophotometry were used in this analysis. Pulsed Excimer (UV) laser systems were used to systematically study the efficacy of laser pulses (pulse energy density, wavelength, duration, and power density) to remove tissue from the intima of coronary arteries while minimizing damage to underlying artery wall.

MAJOR FINDINGS: Data reveal that the carbon dioxide laser can cut experimentally created membranes in rabbits for virtually any condition of the clarity of the optical media. The Nd:YAG laser pulses can cut vitreal membranes when power densities exceeding 1 GW/cm^2 are achieved at the target. Moderate to severe turbidity of the optical media greatly decreases the ability to cut vitreal membranes with the Nd:YAG laser and creates the potential for increased retinal damage. The Nd:YAG laser can not be used within 2 mm of the retina without significant risk of retinal damage due to the absorption of radiation by the outer retina. The CO_2 laser systems can be used within 2 mm of the retina safely only when short duration pulses are used at a slow repetition rate in order to prevent the establishment of convective currents of hot vitreous. The CO_2 laser is appropriate for cutting vascular membranes due to thermal coagulation of blood vessels accompanying the cutting action, whereas the use of the Nd:YAG laser in these cases without previous coagulation of vessels would result in vitreal hemorrhage. A prototype CO_2 laser system of the above design is currently being use in human clinical trials at the Cleveland Clinic (S. Meyers). Preliminary results on human coronary arteries in vitro suggest that only highly absorbed radiation in submillisecond pulses (e.g., pulsed CO_2 laser or Q-switched KrF laser) offers the potential for such highly specific (local) laser microsurgery.

SIGNIFICANCE: Although the present mechanical vitrectomy instruments perform well in most cases, there is a risk of intraoperative complications (retinal tears and hemorrhage) when vitreal membranes are cut, especially if the membranes are taut and have a strong adhesion to the retina. "Tension" on the membranes is increased as the "cutter" of the vitrectomy instrument or the vitreous scissors cuts the tissue. This tension is transmitted to the vitreoretinal adhesion and surrounding retina predisposing this area to hemorrhage and retinal tears. If the vitreal membrane is vascularized, this tension may cause bleeding. The carbon dioxide laser vitrectomy may decrease the incidence of these intraoperative complications and increase facility in cutting selected vitreal membranes.

The fiber optic delivery system for the CO_2 energy as well as the specific laser pulse pattern developed for optimal cutting of vitreous bands without damaging surrounding eye tissues may be generally applicable to all types of CO_2 laser surgery. The combined illumination-irrigating 20 gauge probes have improved the currently available instrumentation available for vitreous surgery.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 RS 10099-05 BEI
PERIOD COVERED October 1, 1984 to September 30, 1985		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Cochlear Mechanics and Hair Cell Transduction		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) R.S. Chadwick, Biomedical Engineer BEIB, DRS J. Rinzel, Chief MRB, NIADDK S. Shamma, Assistant Prof. Univ. of MD, Dept. of Electrical Engineering J. Wilbur, Staff Fellow, MRB, NIADDK K. Morrish, Staff Fellow MRB, NIADDK		
COOPERATING UNITS (if any) NIADDK, Mathematical Research Branch Univ. of Maryland, Dept. of Electrical Engineering		
LAB/BRANCH Biomedical Engineering and Instrumentation Branch		
SECTION Mechanical Engineering		
INSTITUTE AND LOCATION DRS, National Institutes of Health, Bethesda, MD 20205		
TOTAL MAN-YEARS: 0.25	PROFESSIONAL: 0.25	OTHER:
CHECK APPROPRIATE BOX(ES) ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither ☐ (a1) Minors ☐ (a2) Interviews		
SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.) A mathematical model of cochlear processing is developed to account for the nonlinear dependence of frequency selectivity on intensity in inner hair cell and auditory nerve fiber responses. The model describes the transformation from acoustic stimulus to intracellular hair cell potentials in the cochlea. It incorporates a linear formulation of basilar membrane mechanics and subreticular fluid-cilia displacement coupling, and a simplified description of the inner hair cell nonlinear transduction process. The analysis at this stage is restricted to relatively low frequency single tones. The computed responses to single tone inputs exhibit the experimentally observed nonlinear effects of increasing intensity such as the increase in the bandwidth of frequency selectivity and the downward shift of the best frequency. In the model the first effect is primarily due to the saturating effect of the hair cell nonlinearity. The second results from the combined effects of both the nonlinearity and the inner hair cell lowpass transfer function. In contrast to these shifts along the frequency axis, the model does not exhibit intensity dependent shifts of the spatial location along the cochlea of the peak response for a given single tone. The observed shifts therefore do not contradict an intensity invariant tonotopic code.		

Z01 RS 10099-05 BEI

OBJECTIVES: To calculate the electrical signals being transmitted to the brain via the 8th auditory nerve in response to pure and complex sound input in the cochlea.

METHODS EMPLOYED: The appropriate equations of fluid mechanics, solid mechanics, and neurophysiology are solved in a cascaded model of the basilar membrane mechanics, fluid-cilia coupling, and hair cell transduction.

MAJOR FINDINGS: The processing of a single tone has been computed. The calculated dependence of AC and DC hair cell potentials on frequency and stapes amplitude is in general agreement with reported experimental findings. We found that the DC hair cell tuning curve is sharpened by the nonlinear cilia displacement - conductance relation for the hair cell.

SIGNIFICANCE: This is one of the first attempts to coordinate what has been until now two distinct areas of investigation: cochlear mechanics and auditory neurophysiology. Such a combined approach will help to answer some fundamental questions in auditory physiology and in the design of cochlear prostheses, such as the relative importance and interaction of mechanical and neural events in auditory analysis and the relative importance of temporal versus frequency information.

PROPOSED COURSE: We plan to extend the applicability of the model to higher frequency and analyze the processing of more complex input signals.

PUBLICATIONS

Shamma, S.A., Chadwick, R.S., Wilbur, W.J., Rinzel H., and Morrish, K: A biophysical model of cochlear processing. Presented at Acoustical Society Meeting, Norfolk, VA. 1984.

Chadwick, R.S.: Three dimensional effects on low frequency cochlear mechanics. Mech. Res. Comm., in press.

Morrish K., Chadwick, R.S., Shamma, S., and Rinzel, J.: Parameter sensitivity in a mathematical model of basilar membrane mechanics. To appear in Proceedings of 1985 Mechanics of Hearing Workshop, Boston University, Boston, MA, August 1985.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 RS 10103-05 BEI
PERIOD COVERED October 1, 1984 to September 30, 1985		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Triple Laser-Multi Parameter Flow Cytometry System for Study of Tumor Cell Kinetics		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) W. Schuette, Chief, ACES, BEIB, DRS S. Shackney, Allegheny General Hospital, Pittsburgh, PA 15212 J. Dvorak LPD-NIAID F. Plowman, ACES, BEIB, DRS		
COOPERATING UNITS (if any) DRS-NCI LPD-NIAID		
LAB/BRANCH Biomedical Engineering and Instrumentation		
SECTION Applied Clinical Engineering		
INSTITUTE AND LOCATION DRS, National Institutes of Health, Bethesda, MD 20205		
TOTAL MAN-YEARS: 3	PROFESSIONAL: 2	OTHER: 1
CHECK APPROPRIATE BOX(ES) ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither ☐ (a1) Minors ☐ (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) A triple laser flow cytometer has been developed so that various immuno-fluorescent labeling techniques may be employed for the investigation of cell kinetics. Three laser beams at different wave lengths are made to intersect a tumor cell flow stream passing through a quartz cuvette so that multi-parameter signals may be obtained. These signals are processed by specialized electronics and then analyzed by means of a PDP 11 computer. Simplified optics have increased light detection efficiency by an order of magnitude. The system is currently being used for the investigation of a unicellular protozoon known as trypanosoma cruzi, the causative agent of Chagas disease. Electronic cell volume capability has been added to the system to assist in the bivariate analysis of trypanosoma cruzi fluorescence data.		

Z01 RS 10103-05 BEI

PUBLICATIONS

Schuette, W.H., Shackney, S.E., MacCollum, M.A., and Smith, C.A.: A count dependent filter for smoothing flow cytometric histograms. Cytometry 5: 487-493, 1984.

Schuette, W.H., Shackney, F.A., Plowman, F.A., Tipton, H.W., Smith, C.A., and MacCollum, M.A.: Design of flow chamber with electronic cell volume capability and light detection optics for multi-laser flow cytometry. Cytometry 5: 652-656, 1984.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 RS 10109-05 BEI
PERIOD COVERED October 1, 1984 to September 30, 1985		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Adjunct Heat Treatment of Cancer		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) R.L. Levin, Biomedical Engineer, BEIB, DRS M. Hagmann, Senior Staff Fellow, BEIB, DRS J-L Guerquin-Kern, Fogarty Fellow, BEIB, DRS C. Charny, Guest Worker, BEIB, DRS A. Shitzer, Visiting Scientist, BEIB, DRS A. Zabel, Physician, ROB, NCI E.J. Glatstein, Chief, ROB, NCI		
COOPERATING UNITS (if any) Radiation Oncology Branch, NCI		
LAB/BRANCH Biomedical Engineering and Instrumentation Branch		
SECTION Mechanical Engineering Section,		
INSTITUTE AND LOCATION DRS, National Institutes of Health, Bethesda, MD 20205		
TOTAL MAN-YEARS: 3.8	PROFESSIONAL: 3.8	OTHER:
CHECK APPROPRIATE BOX(ES) ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither ☐ (a1) Minors ☐ (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) The purpose of this project is to facilitate the development of adjunct hyperthermia modalities for cancer treatment by theoretically and experimentally studying the spatial and temporal variation in the temperature field of tissues subjected to microwave and radio-frequency electromagnetic radiation. Currently, we are (1) experimentally measuring the patterns of energy deposition within various types of extremity phantoms produced by a Mini Annular Phased Array (MAPA) applicator; (2) theoretically describing the electromagnetic fields of a MAPA in terms of its design parameters; (3) theoretically describing the transient thermal profiles within limbs produced by a MAPA; and (4) theoretically describing the systemic temperature and cardiac changes associated with heating various regions of the body. We are also performing electromagnetic and thermal modeling of the unwanted non-local energy deposition occurring outside the bounds of typical hyperthermia applicators.		

OBJECTIVES:

- (1) To optimize the radiation fields generated by a MAPA applicator.
- (2) To continue to develop a generalized mathematical model which will predict the spatial and temporal variation of the temperature field within a tissue or organ subjected to electromagnetic irradiation.
- (3) To develop optimal adjunct hyperthermia modalities.

METHODS EMPLOYED:

- (1) Mathematical modeling of the radio-frequency and thermal characteristics of various types of phantoms and human extremities subjected to RF irradiation from various types of applicators will be accomplished through the use of ROB's VAX-11/750 computing system and its associated graphics hardware.
- (2) Experimental measurements of the electric field and thermal profiles of various types of phantoms subjected to RF irradiation from various types of applicators will be accomplished through the use of MES/BEIB's PDP-11/34 computing system and its associated data acquisition system and also a BSD-1000 Hyperthermia System.

MAJOR FINDINGS

Our experimental results indicate that a) the MAPA is a broadband device useable at least over the frequency range of 100 to 200 MHz b) For a cylindrical phantom the $|E_z|^2$ distributions are more uniform at the lower frequencies. Inclusion of a concentric bone equivalent phantom moves the contours outward in such a manner that the SAR at the surface of the bone corresponds to that value which had been present on the axis. Lateral displacement of the phantom within the MAPA alters significantly the resulting SAR patterns. The degree of bolus filling also significantly alters the resulting SAR patterns. c) For a single leg phantom, the SAR distribution is skewed towards the pelvis at both low and high frequencies. For the higher frequencies, a secondary maximum is observed at the ankle for a MAPA centered about the knee. d) For a double leg/pelvic phantom, the energy deposition is mostly confined to the leg being treated. The maximum SAR in the untreated leg and the pelvis is less than 10% of that in the area being treated. e) Anatomically shaped phantoms are important for the proper characterization of hyperthermia applicators.

Our RF modeling studies indicate that a) The presence of a wooden gurney and conducting floors/walls/ceilings do not significantly affect the pattern of energy deposition resulting from regional hyperthermia rf applicators. b) A physician standing near a patient being treated with a regional hyperthermia rf applicator may absorb as much as 50% of the energy supposedly being used to heat the patient. c) An isolated double leg/pelvic phantom is suitable for experimental studies of the SAR distribution within the lower half of a complete human body.

Our thermal modeling studies indicate that a) Deep heating of the upper arm to 45.5°C is possible with no apparent physiological abnormalities. b) Abdominal heating with 1 kW can only reach 41°C before dangerous physiological responses are seen. c) When non-local energy deposition is accounted for, abdominal heating is even less effective, with the side effects more severe.

SIGNIFICANCE: At present, the heat treatment of cancerous cells when combined with conventional radiotherapy and chemotherapy shows considerable promise in the management of cancer. Nevertheless, there still remain numerous important problems that must be resolved. Of paramount importance is the problem of generating and controlling uniform temperature fields within tissues. This study will therefore attempt to facilitate the development of optimum hyperthermia modalities by theoretically and experimentally studying the temperature fields within tissues subjected to radio frequency EM radiation.

PROPOSED COURSE:

- (1) To continue the electromagnetic and thermal characterization of phantom combinations using non-perturbing probes.
- (2) To develop a computerized treatment planning system.

PUBLICATIONS

Hagmann, M.J., Calloway, L., Levin, R.L., Smith, S.R., and Forster, R.E.: New muscle equivalent phantom materials for 10-100 MHz. BEMS (1984). Abstract.

Hagmann, M.J., Levin, R.L., and Glatstein, E.J.: Evaluation of patterns of energy deposition using RF applicators for regional hyperthermia. 26th ASTR Meeting (1984). Abstract.

Levin, R.L. and Hagmann, M.J.: A heat and mass transfer model of human extremities during hyperthermia. Med. Phys., (in press).

Hagmann, M.J. and Levin, R.L.: Coupling efficiency of helical coils. IEEE Trans., Biomed. Eng. 32: 539-540, 1984.

Hagmann, M.J. and Levin, R.L.: Convergence of local and average values in three dimensional moment method solutions. IEEE Trans., MTT. 33: 649-654, 1985.

Hagmann, M.J. and Levin, R.L.: Accuracy of block models for evaluation of the deposition of energy by electromagnetic fields. IEEE Trans., MTT (in press).

Hagmann, M.J. and Levin, R.L.: Aberrant heating: a problem in regional hyperthermia" IEEE Trans. on Biomed. Eng. (in press).

Hagmann, M.J., Levin, R.L., and Turner, P.F.: A comparison of the annular phased array with helical coil applicators for limb and torso hyperthermia" IEEE Trans, Biomed. Eng. (in press).

Z01 RS 10109-05 BEI

Guerquin-Kern, J-L, Hagmann, M.J., and Levin, R.L.: Experimental characterization of the BSD-MAPA for extremity heating. Proceedings of the 1985 NAHG Meeting (1985).

Hagmann, M.J., Levin, R.L., and Guerquin-Kern, J-L.: Theoretical characterization of aberrant heat effects. Proceedings of the 1985 NAHG Meeting (1985).

Charny, C.K., Levin, R.L., and Hagmann M.J.: Whole body thermal model of man during hyperthermia. Proceedings of the 1985 NAHG Meeting (1985).

Hagmann M.J., Levin, R.L., and Guerquin-Kern, J-L, Thermal and RF characterization of several applicators for use in hyperthermia. Proceedings of the XVIth Intl. Congress of Radiology (1985).

Hagmann, M.J. and Levin, R.L.: Non invasive determination of local energy deposition from measurements of near fields. Proceedings of Near Field Microwave Imaging Symposium (1985).

Guerquin-Kern, J-L, Hagmann, M.J., and Levin R.L.: Experimental characterization of the BSD MAPA on several shaped leg models with or without perfusion. Proceedings of the VIIth Meeting of the European Society for Hyperthermic Oncology (1985).

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 RS 10110-05 BEI
PERIOD COVERED October 1, 1984 to September 30, 1985		
TITLE OF PROJECT (20 characters or less. Title must fit on one line between the borders.) A Dual 3-Dimensional Position Monitor For Speech Analysis: MOD. II		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) E.C. Walker, Mechanical Engineer, ACES BEIB Other Investigators H.W. Tipton, Mechanical Engineering Tech. ACES BEIB T.L. Talbot, Mechanical Engineer ACES BEIB C.L. Ludlow, LCD NINCDS M. Doran-Quine, Guest Researcher NINCDS		
COOPERATING UNITS (if any) LCD-NINCDS		
LAB/BRANCH Biomedical Engineering and Instrumentation		
SECTION Applied Clinical Engineering		
INSTITUTE AND LOCATION DRS, National Institutes of Health, Bethesda, MD 20205		
TOTAL MAN-YEARS: .5	PROFESSIONAL: .5	OTHER:
CHECK APPROPRIATE BOX(ES) ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither ☐ (a1) Minors ☐ (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) Several speech monitoring instruments have been designed to study the etiology of normal and-abnormal articular movements in humans. The first system, which is in current use, provided a unique method of monitoring 3-D lip and jaw movements. The second system, MOD II, is an improved version of the first. The device consists of two mirror image transducers mounted on a common head frame. Each transducer, which can be individually adjusted, is capable of measuring the movement of a point in three orthogonal planes. The transducers have been structurally and operationally redesigned to provide increased linearity, resolution, and reduced weight. Additionally, the head frame has been totally redesigned to provide improved wearing comfort and reduced weight. The improved system will facilitate studying a broader patient population such as children and the elderly. Design and fabrication of MOD II has been completed. Results of bench tests indicate that the system performs well, within its specified range. Future efforts will be directed toward patient testing. Following system enhancement, patient testing will be scheduled for the upcoming fiscal year. Due to the patient population (which includes dysarthric patients) that this device is designed for, future enhancements will include improved resolution along the lateral-medial axis and reduction of inertial response.		

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 RS 10112-05 BEI

37

PERIOD COVERED

October 1, 1984 to September 30, 1985

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Analysis of Microcirculatory Blood Flow by Laser Doppler Scattering

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

R.F. Bonner, Physicist, BEIB, DRS
T.R. Clem, Elect. Engineer, BEIB, DRS
M. Kaliner, Section Chief LCI NIAID
H. Druce, Clinical Assoc. LCI NIAID
G. Rogers, Clinical Assoc. LCI NIADUK
M. Roy, Visiting Scientist NEI
D. Goldstein, Sr. Invest. HB NHLBI; H. Kaiser, Chief HB NHLBI
E. Oldfield, Neurosurgeon SN NINCDS; R. Blacklock, Clinical Assoc. SN NINCDS

COOPERATING UNITS (if any)

Hypertension Br., NHLBI; Lab of Clinical Investigation, NIAID; Lab of Chemical Biology, NIADDK; Surgical Neurology, NINCDS; Clinical Branch, NEI; MED Pacific, Inc. Seattle, Washington; TSI, St. Paul Minn.

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Electrical and Electronic Engineering

INSTITUTE AND LOCATION

DRS, National Institutes of Health, Bethesda, MD 20205

TOTAL MAN-YEARS:

1.6

PROFESSIONAL:

1.6

OTHER:

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unlined type. Do not exceed the space provided.)

The purpose of this project is the development of a clinical, non-invasive monitor of tissue blood flow by analysis of the spectrum of Doppler-scattered laser light. The NIH Laser Doppler Blood Flow Monitor has been demonstrated to be highly portable and clinically convenient with sterilizable, rugged flexible 4m fiber optic probes and portable photodiode detection system. The linearity of the flow analysis processor has been demonstrated in a variety of tissues and clearly resolves physiologic flow changes including pulsatile flow in the microcirculation. Muscle blood flow in over 50 patients with neuromuscular disease has been studied and data suggest that post occlusive reactive hyperemia responses may be primary or secondary indicators of disease state. Measurements of local muscle blood flow dynamics in patients with neuromuscular diseases indicate abnormalities distinct to different disease types. Nasal blood flow has been shown to be a quantitative measure of the physiologic response of the nose to drug challenges. Brain and spinal cord blood flow measurements during microsurgery has been shown to be feasible in two patients and provides the surgeon with potential for useful evaluation of his surgical procedures as well as for furthering understanding of microcirculatory dynamics in neural tissue. Studies show a characteristic local oscillatory flow pattern in a capillary microcirculation of the skin in sickle cell patients which appears to correlate with severity of disease and its response to drug therapy. Similar oscillations presumably due to myogenic arteriolar smooth muscle vasomotion are characteristic of several hypertensive patients, particularly those on drugs inducing peripheral vasoconstriction. Preliminary studies on patients with Type I diabetes have shown abnormalities potentially related to the etiology of the microvascular component of long-term type I diabetes. In summary numerous ongoing clinical studies seek to characterize microvascular functional abnormalities and their role in a number of diseases with microvascular components.

GPO 814-818

OBJECTIVES: Ongoing clinical applications include brain and spinal cord blood flow during surgery, skin blood flow in normal, hypertension, diabetes, sickle cell disease, cold urticaria and scleroderma patients and nasal blood flow responses to drug and antigen challenge in normals and rhinitics. Specific objective at this stage is the application of the instrument and technique in the above variety of clinical and experimental problems. Assistance to the commercial manufacturers (Med Pacific and TSI) is being provided to insure a high quality commercial instrument.

METHODS EMPLOYED: The present form of the apparatus has demonstrated its clinical convenience and portability. Minor modifications to probe tip are made for specific applications. Methodologies for clinical diagnosis are developed in collaboration with clinicians. The modifications suggested and implemented in the commercial instrument design are based on spectral noise analysis and theoretical analysis of the method.

MAJOR FINDINGS: (1) The commercial models have been dramatically upgraded to performance comparable to NIH prototype. The mean frequency detection scheme and fiber optic system developed at NIH has been implemented in all commercial devices. A new blood volume measuring circuit has been implemented in the NIH prototype and in some commercial versions. (2) A rigorous scattering theory substantiates the validity of our analysis method as do empirical correlations with alternative techniques. The instrument output conversion of 1 volt - 15 ml/min/100gm tissue holds with small variations for very different tissue types. (3) Measurements of local muscle blood flow dynamics in patients with neuromuscular diseases indicate abnormalities distinct to different disease types. (4) Scleroderma patients fingertip blood flow appears to fall in three easily-discernable classes associated with the severity of the disease and a simple measurement protocol may elucidate efficacy of drug therapy. (5) Nasal blood flow has been shown to be sensitive to allergic state and various nasal challenges; analysis of blood volume, flow and mean speed has contributed to understanding nasal physiology. (6) Studies show a characteristic local oscillatory flow pattern in a capillary microcirculation of the skin in sickle cell patients. (7) Studies in selected hypertensive patients have provided additional evidence for rhythmic fluctuations in myogenic tone of arteriolar smooth muscle as a physiologic regulator of microcirculatory flow. (8) Spinal cord blood flow during AVM repair demonstrated the positive effects of surgery as well as indicating significant anterior vasoconstriction in neural tissue.

PROPOSED COURSE: Pursue clinical trials to establish the instrument as a useful clinical and experimental tool.

SIGNIFICANCE: The NIH Laser Doppler Blood Flow Monitor is an instrument which holds great promise for study of the local tissue microcirculation. It has potential applications in the research laboratory, and in the clinical study of scleroderma, sickle cell disease, hypertension, diabetes, peripheral vascular disease, allergy testing, screening of vaso-active drugs, and the monitoring of patients with burns and skin grafts.

Z01 RS 10112-05 BEI

PUBLICATIONS:

Druce, H.M., Bonner, R.F., Choo, P., Patow, C., Summers, R., and Kaliner, M.A.: Response of nasal blood flow to neurohormones as measured by laser-doppler velocimetry. J. Appl. Physiol. 57: 1276-83, 1984.

Rodgers, G.P., Schechter, A.N., Noguchi, C.T., Klein, H.G., Nienhuis, A.W., and Bonner, R.F.: Periodic microcirculatory flow in patients with sickle cell disease. N. Engl. J. Med. 311 :1534-8, 1984.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER ZO 1 RS 10116-04 BEI
PERIOD COVERED October 1, 1984 to September 30, 1985		
TITLE OF PROJECT (60 characters or less. Title must fit on one line between the borders.) Modeling of Arterial Pulse Waves		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
R.S. Chadwick, Biomedical Engineer, BEIB, DRS D. McGuire, Mathematician, BEIB J. Tenney, Biomedical Engineer BEIB D. Goldstein, Senior Investigator EHL, NHLBI H. Kaiser, Chief EHL, NHLBI		
COOPERATING UNITS (if any) NHLBI, Endocrine-Hypertension Laboratory		
LAB/BRANCH Biomedical Engineering and Instrumentation		
SECTION Mechanical Engineering Section		
INSTITUTE AND LOCATION DRS, National Institutes of Health, Bethesda, MD 20205		
TOTAL MAN-YEARS: .6	PROFESSIONAL: .3	OTHER: .3
CHECK APPROPRIATE BOX(ES) ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither ☐ (a1) Minors ☐ (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) A pulse wave theory and a model of the human brachial arterial system is developed that predicts the changes in the arterial pressure waveforms as it traverses the vasculature - increased pulse, sharper main wave, disappearance of the aortic incisura, and appearance of a diastolic dicrotic wave. It also predicts the observed modulation of the waveform during phenylephrine - induced vasoconstriction and nitroglycerin - induced vasodilation. The model considers the brachial arterial system as a tapered distensible tube ending in a loop, with side branch networks represented by distributed Windkessels, and it uses verifiable values for realistic parameters. We found that the vertical modulation of the dicrotic wave in people decreased with advancing age and with high blood pressure, the model explaining these finding in terms of increasing vascular rigidity and decreasing small vessel vasodilator responsiveness. We noted a significant negative correlation between the arterial level of plasma norepinephrine and the amount of modulation of the dicrotic wave after nitroglycerin among subjects 40 years old or younger, suggesting a sympathetic neurogenic contribution to the vascular abnormalities observed in relatively young patients with essential hypertension.		

Z01 RS 10116-04 BEI

OBJECTIVES: To establish the mechanisms that are responsible for the clinically observed reduced dicrotic wave modulation of young hypertensive subjects in response to vasoactive drugs.

METHODS EMPLOYED: The new theory developed to deal with wave propagation in a branching system has been implemented for a efficient numerical computation of pressure and flow waveforms as well as frequency analysis of vascular impedance. The basic computation is done in the frequency domain, and periodic waveforms are computed using Fourier synthesis.

MAJOR FINDINGS: We found that very realistic pressure waveforms can be computed with this theory. To simulate the clinically observed modulation of the dicrotic wave, it is necessary to change both the main branch wave speed and the side branch network resistance and compliance.

SIGNIFICANCE: The theoretical work described here leads to the suggestion that defective modulation of the dicrotic wave with age and high blood pressure result from a combination of increased large vessel stiffness and decreased vasodilator capacity. Such a finding helps to identify both the sites and modes of action of vasoactive drugs as well as clarifying the fundamental processes in the control of blood pressure. The approach used in the present study represents one of the first attempts to use a circulatory model to explain abnormalities in the contour of the pressure waveform in hypertension.

PROPOSED COURSE: Measurements of brachial artery blood flow and arterial distensibility are planned to further validate our present views on dicrotic wave modulation. Computer algorithms are being written and tested that attempt to automate the determination of the optimal parameter set for the mathematical model.,

PUBLICATIONS

Chadwick, R.S.: Pulse wave propagation in an artery with leakage into small side branches, Proc. Nat. Acad. Sci. (in press).

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 RS 10122-04 BEI
PERIOD COVERED October 1, 1984 to September 30, 1985		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Micro-computer Controlled Fermentation System		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) T.R. Clem, Sr., Electronic Engineer, EEES, BEIB, DRS Other Investigators: Y. Shiloach Chief, Pilot Plant LCDB NIADDK A. LeRoy Chemical Engineer BEIB, DRS		
COOPERATING UNITS (If any) LCDB - NIADDK		
LAB/BRANCH Biomedical Engineering and Instrumentation Branch		
SECTION Electrical and Electronic Engineering Section		
INSTITUTE AND LOCATION DRS, National Institutes of Health, Bethesda, MD 20205		
TOTAL MAN-YEARS: 1.0	PROFESSIONAL: 0.5	OTHER: 0.5
CHECK APPROPRIATE BOX(ES) ☐ (a) Human subjects ☐ (a1) Minors ☐ (a2) Interviews ☐ (b) Human tissues ☐ (c) Neither		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) A process control system using a Personal Computer as the central control element is continuing to be developed for the NIH Fermentation Pilot Plant. The various monitoring transducers and controlled elements (pumps, valves, etc.) are connected to the computer via the IEEE-488 General Purpose Interface (GPIB) and special purpose interface cards. For maximum versatility most components used are commercially available items (instruments, meters, etc.). The PC-based design allows changes in the parameters measured or controlled, or scaling to different size vessels to be accomplished relatively quickly and easily. Utilizing the computational capabilities of the computer/controller allows initial selection of the operating parameters and dynamic alteration of these parameters as the process continues, thus allowing optimization of yields or detailed study of the process parameters.		

Z01 RS 10122-04 BEI

OBJECTIVE: Increase efficiency and productivity of the Pilot Plant Unit, expand fermentation process capability, and improve methods whereby research into the fermentation process can be performed by implementing a computer-controlled process control system.

METHODS EMPLOYED: A desktop Personal Computer and an electronic interface system are connected to both new and previously-owned laboratory instruments and to a fermentation vessel via the IEEE-488 GPIB or direct electrical connections. The interface scheme is versatile enough to allow changes to be made to the system rather easily. The control programs are written in a high level language, such as BASIC or PASCAL, which facilitate understanding and modification by the user.

SIGNIFICANCE: Computer monitoring and controlling of the fermentation process produces several significant advantages over manual methods. By using the computer to make decisions based on what is occurring in the fermentation process, parameters can automatically be altered to either produce an increased yield of a particular product, produce a purer form of the product, or study the effects on a particular product of the alteration of selected parameters. The computer can also perform some of the "housekeeping" tasks associated with running a fermentation process that would normally occupy an operator. The computers acquisition and computational capabilities allows growth rate to be assessed under a variety of environmental conditions.

PROPOSED COURSE: To continue expanding and refining the system to provide additional functions, monitor and control additional parameters, and implement more sophisticated control programs to expand operation of the system. Larger fermentation vessels are being acquired by the pilot plant which include more modern instrumentation devices and these will be interfaced with our computer system.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 RS 10143-04 BEI
PERIOD COVERED October 1, 1984 to September 30, 1985		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Interaction of Body Temperature and Sleep Rhythms		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) T.L. Talbot, ACES, BEIB, DRS Wallace Mendelson, Psychobiology, NIMH		
COOPERATING UNITS (if any) Psychobiology Lab-NIMH		
LAB/BRANCH Biomedical Engineering and Instrumentation		
SECTION Applied Clinical Engineering		
INSTITUTE AND LOCATION DRS, National Institutes of Health, Bethesda, MD 20205		
TOTAL MAN-YEARS: 0.5	PROFESSIONAL: 0.5	OTHER:
CHECK APPROPRIATE BOX(ES) ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither ☐ (a1) Minors ☐ (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) Clinical evidence suggests a correlation between <u>core body temperature</u> and the frequency of <u>sleep episodes</u>. An artificial <u>thermoregulatory system</u> is completed which will permit <u>core body temperature manipulation</u> and hence, the evaluation of the efficacy of <u>thermal regulation in the treatment of sleep disorders</u>. Clinical trials are now performed on a regular basis. Simultaneous <u>sleep recordings</u> are obtained during both a non-manipulated and manipulated 24 hour period. Clinical studies are now underway and the data obtained so far suggests no interaction between <u>sleep rhythms</u> and <u>body temperature</u>. More studies are being performed to substantiate conclusively these findings. Reevaluation of clinical evidence has prompted an extensive effort to accumulate a larger, more complete data base of control subjects. <u>Standard sleep recordings</u> and <u>temperature profiles</u> of normal subjects are being taken before further intervention protocols are implemented.		

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 RS 10146-03 BEI
PERIOD COVERED October 1, 1984 to September 30, 1985		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Prosthetic Urethral Sphincter		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) S. B. Leighton, Mechanical Engineer, BEIB, DRS, Steven Scoog, M.D. WP JMC T. Rade Baugh, BRCM, NIA		
C/O OPERATING UNITS (If any) BRCM, NIA DCT, NCI		
LAB/BRANCH Biomedical Engineering and Instrumentation Branch		
SECTION Mechanical Engineering Section,		
INSTITUTE AND LOCATION DRS, National Institutes of Health, Bethesda, MD 20205		
TOTAL MAN-YEARS: .05	PROFESSIONAL: .05	OTHER: 0
CHECK APPROPRIATE BOX(ES) ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither ☐ (a1) Minors ☐ (a2) Interviews		
SUMMARY OF WORK (Use standard un-reduced type. Do not exceed the space provided.) A number of techniques are used for treating urinary incontinence, including a number of artificial prosthetic sphincters. The present work concerns an entirely intraurethral artificial sphincter that can be implanted without surgery. Concepts are being explored which would allow the device to be used in situations in which surgery is contraindicated, and would also presumably lower the cost. The valve would be appropriately matched to urethral dimensions, pressures, and flowrates. The valve would be potentially useful in cases of nonopening normal valves as well as in cases of non-closing valves.		

OBJECTIVES: To develop and test an artificial prosthetic urethral sphincter that can be introduced non-surgically into the urethra.

METHODS: A large scale model of an artificial valve with appropriate pressure flow characteristics has been designed. It will be bench tested and miniaturized. After thorough and successful bench testing, clinical tests will be designed to verify function and safety.

MAJOR FINDINGS: A physical model has been built and tested. A prototype has been designed.

SIGNIFICANCE: Urinary incontinence affects about 10% of the population over 65, and significant numbers of younger people due to paralysis, infection, and other causes. A simpler, less expensive treatment technique would presumably be useful for at least a reasonable fraction of these cases.

PROPOSED COURSE: Design and bench testing of various valve designs will proceed. Clinical tests will be designed to test proper function and safe operation.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 RS 10151-03 BEI
PERIOD COVERED October 1, 1984 to September 30, 1985		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Nuclear Magnetic Resonance Imaging		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) Dr. David I. Hoult, Physical Scientist, BEIB, DRS Other personnel: Dr. Ching-Nien Chen, Expert Dr. Victor J. Sank, Expert Dr. L. Kyle Hedges, Staff fellow		
COOPERATING UNITS (if any) Department of Radiology, Clinical Center		
LAB/BRANCH NMR Imaging Laboratory, Biomedical Engineering and Instrumentation		
SECTION Office of the Chief		
INSTITUTE AND LOCATION DRS, National Institutes of Health, Bethesda, MD 20205		
TOTAL MAN-YEARS: 3.2	PROFESSIONAL: 3.0	OTHER: 0.2
CHECK APPROPRIATE BOX(ES) ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither ☐ (a1) Minors ☐ (a2) Interviews		
SUMMARY OF WORK (Use standard un-reduced type. Do not exceed the space provided.) Using our previously developed nuclear magnetic resonance imaging equipment, the dependence of the signal-to-noise ratio and radio frequency power deposition in patients, as a function of static field strength, has been investigated, in order to elucidate further the factors influencing the choice of a field strength for clinical imaging. It has been found that power deposition in the torso is reduced by a factor of between 1.5 and 2.5 (depending on patient build) if the irradiating field is applied laterally, as opposed to anterior-posterior, and the signal-to-noise ratio dependence has been shown to be in good agreement with a previously developed theory. Quadrature coil development has progressed well for imaging and for spectroscopy. Improvements have been made, with the aid of pieces of steel, to the homogeneity of the clinical imaging instrument.		

OBJECTIVES: The development of new techniques and the optimization of instrumentation for nuclear magnetic resonance imaging.

METHODS EMPLOYED: A model nuclear magnetic resonance (NMR) imaging system employing a 60 cm i.d. magnet and radio frequency electronics (built in the Biomedical Engineering and Instrumentation Branch) serves as a versatile test bed, together with standard electronic laboratory instrumentation, for the attainment of the objectives. During the period of the present report, research has centered on the power deposited in a patient during the course of the imaging experiment and the question of the existence of an optimal field strength. To this end, a variety of coils for head and torso operating at frequencies up to 130 MHz have been constructed.

MAJOR FINDINGS: It has been shown that the avoidance of chemical shift artifacts in images necessitates, with present techniques, an increase in r.f. power as at least the third power of frequency. Thus power deposition in the human torso can exceed recommended values at field strengths greater than about 1 Tesla, thereby restricting the versatility of the method. It has also been shown that placing the irradiating magnetic field in a lateral direction, rather than anterior posterior, reduced the power deposition by a factor of between 1.5 and 2.5, depending on a person's shape.

A practical implementation of quadrature coils, for use with the head up to 64 MHz, has been realized and a novel ring quadrature hybrid developed for interfacing the transmitter, preamplifier and coils.

The Clinical Center's imaging system has had its field increased to 0.5 Tesla. The field's homogeneity was improved at this juncture using pieces of steel within the magnet to obtain a peak-to-peak variation of only 7 p.p.m. in a 30 cm diameter spherical volume.

PROPOSED COURSE: To continue work commenced on the optimization of selective 180° pulses for echo formation, and the formation of two and three dimensional images of cat heads using the rotating frame method of imaging. To investigate use of the latter in conjunction with a permanent magnet.

PUBLICATIONS

Hoult, D.I., Chen, C-N., and Sank, V.J.: Quadrature detection in the laboratory frame. Magn. Reson. Med. 1: 339-353, 1984.

Chen, C-N., Hoult, D.I., and Sank, V.J.: A parallel algorithm for rotating frame zeugmatography. Magn. Reson. Med. 1: 354-360, 1984.

Silver, M.S., Joseph, R.I., and Hoult, D.I.: Highly selective $\pi/2$ and π pulse generation. J. Magn. Reson. 59: 347-351, 1984.

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Silver, M.S., Joseph, R.I., Chen, C-N., Sank, V.J., and Hoult, D.I.: Selective population inversion in NMR. Nature 310: 681-683, 1984.

Silver, M.S., Joseph, R.I., and Hoult, D.I.: Selective spin inversion in NMR and coherent optics through an exact solution of the Bloch-Riccati equation. Phys. Rev. A 31: 2753-2757, 1985.

Hoult, D.I. and Lee, D.: Shimming a superconducting NMR imaging magnet with steel. Rev. Sci. Instrum. 56: 131-135, 1985.

Dwyer, A.J., Knop, R., and Hoult, D.I.: Frequency shift artifacts in MRI. J. Comp. Ass. Tomog. 9: 16, 1985.

Hoult, D.I.: Field, sensitivity and contrast in NMR imaging. In James, T.L., and Margulis, A.R. (Eds.): Biomedical Magnetic Resonance. San Francisco, Radiology Research and Education Foundation, 1984, pp. 35-45.

Hoult, D.I.: The sensitivity of the NMR imaging experiment. Proceedings of the NATO Advanced Study Institute: NMR in Living Systems, Palermo, Italy, 1984.

Sank, V.J., Rosenberg, M.L., Chen, C-N., Hoult, D.I., and Eden, H.: Fast access of extended memory for NMR imaging. Proceedings of the DECUS Society, 1984, p. 415.

ABSTRACTS

Chen, C-N., Hoult, D.I., and Sank, V.J.: A parallel algorithm for rotation frame zeugmatography. Magn. Reson. Med. 1: 50, 1984.

Sank, V.J., Chen, C-N., Hoult, D.I., and Eden, H.: Magnetic field stabilization. Magn. Reson. Med. 1: 178, 1984.

Hoult, D.I., Chen, C-N., and Sank, V.J.: Quadrature detection coils - a further $\sqrt{2}$ improvement in sensitivity. Magn. Reson. Med. 1: #92, 1984.

Hoult, D.I., Chen, C-N., and Sank, V.J.: Rotating frame zeugmatography. Magn. Reson. Med. 1: 93, 1984.

Silver, M.S., Joseph, R.I., and Hoult, D.I.: Selective pulse creation by inverse solution of the Bloch-Riccati equation. Magn. Reson. Med. 1: #242, 1984.

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INVITED PRESENTATIONS

D. Hoult

Society of Magnetic Resonance in Medicine, 4th Annual Meeting, London, UK NATO
Summer School, Palermo, Italy, (3 talks)
University of California, Davis
National Bureau of Standards, Gaithersburg, MD
University of Florida, Gainesville, FL
University of Maryland, College Park, MD
European Workshop on NMR Imaging, Copenhagen, Denmark (3 talks)
NATO Summer School, Erice, Italy

C-N Chen

26th Experimental NMR Conference Asilomar, CA
Society of Magnetic Resonance in Medicine, 4th Annual Meeting, London, UK

K. Hedges

Medical Radiologic Imaging Center of the University of Tennessee, Knoxville,
TN
Society of Magnetic Resonance in Medicine, 4th Annual
Meeting, London, UK

V.J. Sank

American Association for Medical Instrumentation Meeting, Boston, MA
Society of Magnetic Resonance in Medicine, 4th Annual Meeting, London, UK
Georgetown University Medical School

AWARD

D.I. Hoult was given the Director's Award, N.I.H.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 RS 10153-03 BEI
PERIOD COVERED October 1, 1983 to September 30, 1984		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) A Position Sensor for Computer Modeling		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) H. E. Cascio, Electronic Engineer, BEIB, DRS P. Smith, Physicist, BEIB, DRS S. Leighton, Mechanical Engineer, BEIB, DRS R. Feldmann, CCB DCRT		
COOPERATING UNITS (if any) CCB, DCRT		
LAB/BRANCH Biomedical Engineering and Instrumentation Branch		
SECTION Electrical and Electronic Engineering		
INSTITUTE AND LOCATION DRS, National Institutes of Health, Bethesda, MD 20205		
TOTAL MAN-YEARS: 0.50	PROFESSIONAL: 0.20	OTHER: 0.30
CHECK APPROPRIATE BOX(ES) ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither ☐ (a1) Minors ☐ (a2) Interviews		
SUMMARY OF WORK (Use standard unredacted type. Do not exceed the space provided.) For the study of macromolecular structure and of molecular interactions, the use of a computer generated display of the molecule is a powerful interpretive tool. In particular, the ability to be able to manipulate in space, i.e. to rotate and translate the molecule(s) to any desired orientation enhances the usefulness of the device. A further degree of sophistication is to provide a feedback mechanism giving an indication of the repulsive or attractive forces (Van der Waals interactions) present as two molecules are fitted together or as a single molecule is twisted to a new conformation. A joy stick apparatus has been designed to provide these features. Two molecules or part of the same molecule can then be rotated and translated in any direction. With each new position, the computer program re-evaluates the appropriate forces to provide the investigator with a feel of the total forces involved.		

OBJECTIVES: To produce a device as an instructive aid in the study of macromolecular structures and of molecular interactions; and also to provide the investigator with the feel of repulsive or attractive forces between molecules.

METHODS EMPLOYED: An Apollo computer model DPS80 will be interfaced to a control gantry. The control gantry, placed in front of a display monitor, will have two joy sticks positioned side by side and supported in space with eighteen connecting lines (nine lines per joy stick). Each line is terminated on a shaft of one of eighteen motors. A joy stick represents a molecule in space and any change in the position of the joy stick will cause the computer program to cause a corresponding position change to the displayed molecule. Each connecting line to the joy stick will be appropriately placed to provide rotational and translational information to the computer. The computer program will calculate and then will initiate the proper current to the appropriate motor, thereby exerting a force on the connecting lines of the joy stick. This exerted force on the joy stick provides the investigator with the feel of molecular forces involved.

Two electronic units will contain the interface and control circuitry for the system. The control circuitry will sense the displacement of the joy stick by counting the pulses generated by the motor shift encoders and supply the motor drive current as determined by the eighteen D/A converters.

SIGNIFICANCE: The study of macromolecular and of molecular interaction becomes more informative while observing the molecular orientation and feeling the appropriate forces involved.

PROPOSED COURSE: The fabrication of the system hardware has been completed and connected to the Apollo computer. Test and evaluation of the compatibility between the hardware and the computer were found to be operational. The testing of the system software is in progress.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 RS 10156-03 BEI
PERIOD COVERED October 1, 1984 to September 30, 1985		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Differential Scanning Calorimeter		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) C.P. Mudd, Biomedical Engineer, ACES, BEIB, DRS T. Talbot, Mechanical Engineer, ACES, BEIB, DRS P.D. Ross, Physical Chemist, A LMB, NIADDK		
COOPERATING UNITS (if any) A LMB, NIADDK		
LAB/BRANCH Biomedical Engineering and Instrumentation		
SECTION Applied Clinical Engineering		
INSTITUTE AND LOCATION DRS, National Institutes of Health, Bethesda. MD 20205		
TOTAL MAN-YEARS: 0.2	PROFESSIONAL: 0.2	OTHER:
CHECK APPROPRIATE BOX(ES) ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither ☐ (a1) Minors ☐ (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) The application of sensor design and modelling techniques from earlier work in differential heat conduction calorimeters to DSC (differential scanning calorimeters) has produced a prototype DSC with a 10 fold effective increase in sensitivity. The effective increase in sensitivity is due to two factors: 1) new thermopile design with increased electrical sensitivity, and 2) improved cell mounting techniques, which increased the common mode rejection of the system. A four channel laboratory instrument based on this prototype design is now being fabricated and will be evaluated in late 1985.		

OBJECTIVES To scan or change the temperature of a sample and observe small changes in the heat content of the sample which are attributed to physical changes within the sample (e.g. conformational changes in proteins) and not the scanning rate. In the laboratory version of the prototype DSC, four active channels will be used; it will accommodate 3 samples and the reference. This will allow 3 simultaneous runs. The objective in this design is to make each of the channels identical so that any one can be used as the reference without degrading the common mode rejection of the other three.

SIGNIFICANCE: The increasing use of DSC in biological work is an indication of its importance in determining the energy levels involved in the conformation changes of large biological molecules. The sensitivity of current instruments limits their use to applications involving relatively large amounts of heat. The combination of sensor and cell mount redesign has increased the effective differential sensitivity by a factor of 10. The 3 sample capability (plus reference) will increase the efficiency of this system by a factor of 3 over the traditional DSC.

PROPOSED COURSE: Previous work in heat conduction calorimeters revealed that the largest contribution to differential noise in the system was the non-repeatability of the cell location in the cell holder. This is also true in DSC. In this new design, the cell location is controlled by locating guides in the cell holder. Keithley 181 nanovoltmeters will be used to measure the three differential signals. This instrument will be fabricated in summer 1985 and evaluated Fall 1985.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 RS 10157-03 BEI
PERIOD COVERED October 1, 1984 to September 30, 1985		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Temperature Controlled Chamber for X-ray Diffraction Specimens		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) C.P. Mudd, Biomedical Engineer, ACES, BEIB, DRS H.W. Tipton, Mechanical Engineering Tech., ACES, BEIB, DRS A.V. Parsigian, Researcher, CR, PSL B.K. Lee, Researcher, CR, PSL D. Rau, A, LCP		
COOPERATING UNITS (if any) DCRT, CR-PSL		
LAB/BRANCH Biomedical Engineering and Instrumentation		
SECTION Applied Clinical Engineering		
INSTITUTE AND LOCATION DRS, National Institutes of Health, Bethesda, MD 20205		
TOTAL MAN-YEARS: 0.2	PROFESSIONAL: 0.2	OTHER:
CHECK APPROPRIATE BOX(ES) ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither ☐ (a1) Minors ☐ (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) A prototype chamber was constructed of lexan and aluminum with a beryllium window to allow the entry of the x-ray beam. The cell containing the specimen is loaded into a holder next to the window. The bottom of the holder is held in contact with one side of a Peltier solid state heat pump. The opposite side of the heat pump is clamped to the aluminum bottom of the chamber which serves as the heat sink. In this early version, a thermistor was used to control the heat pump to keep the specimen at the set temperature. The film plate is mounted inside the chamber on an adjustable slide. Based on the performance of this prototype, two chambers with different focal lengths were requested. The new units were designed with an improved temperature controller. The new unit incorporates a linear feedback sensor with a bipolar supply to allow automatic switching from cooling to heating. The set temperature is fixed by a 3 digit thumbwheel switch and the sample temperature is read out on a 3 1/2 digit display. This new system will hold the sample temperature between -3°C and 85°C with a stability of $\pm 0.02^\circ\text{C}$.		

Z01 RS 10157-03 BEI

OBJECTIVES: There are four objectives:

- (1) To reduce the temperature-motion artifacts of the sample which tend to blur the x-ray pattern.
- (2) To reduce the scattering of the x-rays caused by the air molecules between the sample and the film plate.
- (3) To control the specimen temperature near ambient temperatures by use of a bidirectional heat pump which can shift quickly from cooling to heating or vice-versa.
- (4) To reduce user controls to a minimum and to fix the temperature quickly and accurately.

SIGNIFICANCE: The control of the sample temperature and reduction in the air scattering has yielded dramatic increases in the reproducibility and clarity of the diffraction images. In this design, there is only one beryllium window between the sample and the film plate. The addition of two more sizes will expand the range of patterns that can be investigated. The use of a linear feedback sensor in the controller keeps the loop gain more nearly constant and results in greater stability of the set temperature range.

PROPOSED COURSE: The new chambers have been designed and fabricated. The new controller has been designed and will be fabricated in Summer 1985. Anticipated date of first functional unit, June 1985 with final unit functional in August 1985.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 RS 10159-04 BEI
PERIOD COVERED October 1, 1984 to September 30, 1985		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Pathophysiology of Cachexia in Sarcoma Patients		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) R. Corsey, Electronic Engineer BEIB, DRS J.A. Norton Section Chief SURG, NCI R. Inculet, Research Associate, NCI		
COOPERATING UNITS (if any) Anesthesia Service, Clinical Center, NIH Nutrition Department, Clinical Center, NIH		
LAB/BRANCH Biomedical Engineering and Instrumentation		
SECTION Applied Clinical Engineering		
INSTITUTE AND LOCATION National Institutes of Health, Bethesda, MD 20205		
TOTAL MAN-YEARS: 2.0	PROFESSIONAL: 1.5	OTHER: 0.5
CHECK APPROPRIATE BOX(ES) ☐ (a) Human subjects ☐ (a1) Minors ☐ (a2) interviews ☐ (b) Human tissues ☐ (c) Neither		
SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.) 9 volunteers and 5 patients have been studied. The goal is to study 30 volunteers and 20 patients after which the following questions will be asked: 1. Are patients with preoperative sarcoma different from controls with respect to resting energy expenditure, glucose oxidation whole body protein turnover and k90 levels different in preoperative sarcoma patients from controls? 2. Do differences detected correlate with tumor size or tumor protein fractional synthesis rate? 3. Do differences detected disappear with resection of the tumor? Patients and volunteers are seen by a dietitian who performs a nutritional assessment and estimation of resting energy expenditure. Calorimetry, mass spectrometry and k40 determinations using a whole body counter are performed preoperatively. Protein metabolism and muscle and tumor fractional synthesis rates are measured using ¹³C-leucine and ¹⁵N-glycine.		

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 RS 10162-03 BE I
PERIOD COVERED October 1, 1984 to September 30, 1985		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Wound Healing: Biology and Rheology		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) Thomas L. Talbot, MS, ACES, BEIB Walter T. Lawrence M.D., C. Surgery, NCI Lawrence E. Thibault, ScD. Bioengineering Dept, Univ. of Pa		
COOPERATING UNITS (if any) NCI, University of Pa, Philadelphia, Pa		
LAB/BRANCH Biomedical Engineering and Instrumentation		
SECTION Applied Clinical Engineering Section		
INSTITUTE AND LOCATION DRS, National Institutes of Health, Bethesda, MD 20205		
TOTAL MAN-YEARS: 1.2	PROFESSIONAL: 1	OTHER: 0.2
CHECK APPROPRIATE BOX(ES) ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither ☐ (a1) Minors ☐ (a2) Interviews		
SUMMARY OF WORK (Use standard unredacted type. Do not exceed the space provided.) Preliminary studies have been completed with <u>swine models</u>. These studies involved stamping an <u>indelible grid</u> (10cmx10cm) on the <u>skin of the swine</u>, and the excision of a 1 cm by 10 cm strip of the skin out of the grid area, and finally approximating the incision edges with silk sutures. Photographs of the grid were taken before excision, after excision, and after suturing. These photographs will be analyzed to determine the <u>impressed strain</u> on the wound closure and eventually relate this information to <u>wound breaking strength (WBS)</u>. Studies based on a <u>rat model</u> that relate <u>biologic</u> and <u>pharmacologic</u> interventions to <u>WBS</u> have been completed. Certain groups were treated pharmacologically during the <u>wound healing</u> process. Significant decrease in WBS was observed in these groups as compared to control groups. Further studies will include the comparison of tumor bearing group to control groups. Rats treated with 8 mg/kg <u>Adriamycin</u> prior to or on the day of wounding demonstrated decreased <u>wound breaking strength</u> in incisional wounds at all intervals after wounding. Decreased amounts of <u>collagen</u> and <u>DNA</u>, lower mitotic rates, and decreased cellularity were noted in wound chambers from rats treated in this manner. In both the <u>incisional wound</u> and <u>wound chamber models</u>, rats treated with Adriamycin seven days after wounding showed a less dramatic healing impairment. No differences in collagen type were noted between chambers from the Adriamycin treated and untreated rats. The data suggest that deficient quantities of platelet, macrophage, and lymphocyte factors; a decreased rate of collagen synthesis, and impaired collagen remodelling all contribute to the <u>Adriamycin induced healing impairment</u>.		

Z01 RS 10162-03 BEI

Wound healing was examined in two wound healing models in control rats and animals bearing methylcholanthrene induced sarcomas to evaluate experimentally the effects of tumors on wound breaking strength. In a dorsal incisional wound model, a significant decrease in wound breaking strength was noted from 19 days after the implantation of tumor onward. The size of the breaking strength deficit progressed with the size of the tumor. In a wound chamber model, hydroxyproline levels were measured as an index of collagen content, and ³H-thymidine incorporation was related to DNA content to give an index of DNA synthesis. Histology and collagen types were also examined in the wound chamber model. The tumor bearing state produced no significant change in any of the parameters studied in the wound chambers. The tumor bearing state appears to inhibit wound healing in skin wounds but has no effect on healing in a model of a deeper wound. This difference in healing in the two wound models may be explained by a crosslinking deficiency or differential capacities for healing different types of wounds in tumor bearing rats.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 RS 10163-03 BEI
PERIOD COVERED October 1, 1984 to September 30, 1985		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Magnetoencephalographic Localization of Foci of Neurologic Activity		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
P.D. Smith	Physicist	BEIB, DRS
R.F. Bonner	Physicist	BEIB, DRS
W.S. Friauf	Section Chief	BEIB, DRS
S. Sato	Sr. Investigator	EB NINCDS
R. Porter	Chief	EB NINCDS
M. Nisenoff	Chief	NRL
COOPERATING UNITS (if any) Epilepsy Branch, NINCDS; Naval Research Laboratory		
LAB/BRANCH Biomedical Engineering and Instrumentation Branch		
SECTION Electrical and Electronic Engineering Section		
INSTITUTE AND LOCATION DRS, National Institutes of Health, Bethesda, MD 20205		
TOTAL MAN-YEARS: 1.5	PROFESSIONAL: 0.5	OTHER: 0
CHECK APPROPRIATE BOX(ES) ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither ☐ (a1) Minors ☐ (a2) interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) A continued collaboration with the Naval Research Laboratories has enabled a SQUID magnetometer to be used to study inter-ictal spike discharges in epileptic patients. Correlation of the MEG activity and the corresponding EEG signal for these discharges permits signal averaging of spikes associated with the same neurological event. These measurements allow a magnetic field map at the surface of the scalp to be obtained from which a prediction of the source of the epileptic focus can be made. Computer and electronic processing techniques have been developed to analyze these MEG and EEG signals with the aim of producing an efficient method of localizing the sources of the epileptic discharges in a selective manner. Several patients have been scanned using these techniques. To enhance the collection of MEG data associated with a single spike discharge, a seven channel array detector has been specified and will be installed shortly. Magnetic field maps generated on patients going to surgery predicted epileptic source localization consistent with intraoperative electrical recordings. Refinements of the mapping procedures including MEG normalization by EEG spike amplitude and modeling of contributions of non-sphericity of the scalp over the temporal lobe appear to be substantial improvements in the state-of-the-art.		

Z01 RS 10163-03 BEI

OBJECTIVE: The development of a SQUID magnetic field gradiometer and methodology for its use to localize the three dimensional coordinates of the foci of neurologic activity in the brain particularly those associated with epileptic discharges.

METHODS EMPLOYED: Through collaboration with the Naval Research Laboratory, a single channel second order magnetic field gradiometer has been used to study the MEG signals perpendicular to the surface of the scalp arising from spike discharges in epileptic patients. Simultaneous EEG scalp activity has been monitored using a full set of electrodes. Both MEG and EEG signals were recorded for typically 2 hours per session as the SQUID sensor was positioned across the surface of the scalp. A non-magnetic gantry and bed facilitated this positioning of the sensor with as little inconvenience to the patient as possible. Correlation of the MEG and EEG signals was performed off-line using both a computer and a digital processing oscilloscope. Based on these analyses, real time processing of the MEG and EEG signal has been instigated. Computer modeling of fields produced by a dipole current source within a non-spherical model of each patient's head were correlated with observed MEG maps.

MAJOR FINDINGS: In trying to localize the source of neurologic activity associated with an epileptic spike discharge, the major limitation in producing a magnetic field map required to achieve this goal is the non-reproducible nature of the neurological event being measured. In fact, there are two aspects to this non-reproducibility: firstly, the signal derived from any given inter-ictal discharge is variable, due either to the recruitment of a variable number of neurons cooperating to produce the spike, or alternatively, to a change in orientation within a neuron grouping. A second factor is that in many patients there exist multiple sites of neurological activity each of which elicit an EEG and MEG signal. For these considerations, and based on findings described below using a single sensor, a multiple channel array has been ordered to permit simultaneous position measurements of the MEG signal associated with an individual spike discharge. This array will comprise six 1.5 cm diameter coils arranged in a circle with another single coil at the center; the spacing of the center coil to any of the coils arranged in the circle is 3 cm, and the planes and the coils are arranged on the 10 cm mean radius of the skull. Noise cancellation channels are also to be provided. This detector is at the limit of current sensitivities and represents the maximum number of channels to which present dewar technology can accommodate.

The single channel measurements have been made with the SQUID sensor placed perpendicular and as close as possible to the scalp. In all cases a set of EEG electrodes were present and used as markers of position for the SQUID sensor. A major effort has been to develop a methodology, which is aimed at reducing the time required to scan a patient, to analyze the data so that spikes arising from varied locations can be distinguished; this permits signal averaging techniques to be applied to signals arising from the same location.

These mapping strategies have been developed and tested on patients with epileptic foci. In each patient different focal discharge patterns were identified by multiple EEG recordings. (It is expected that the multiple channel MEG to be installed in summer-fall 1985 will allow discrimination of different focal discharges by the relation of MEG amplitudes among channels.) Signal averaging of MEG responses for each epileptic spike type provided different maps consistent with different discrete foci within a generalized region of the temporal lobe in the patients studied to date. Model analysis based on each patient's skull shape appear to explain the significant deviations of MEG maps from that expected for a simple source within a spherical head. This model and the use of normalization of MEG amplitudes by EEG amplitudes for each spike discharge provides source localization entirely consistent with subsequent intraoperative cortical recordings.

PROPOSED COURSE: To install new state-of-the-art seven channel SQUID system in a manner to optimize data analysis during the patient recording. This system will be directed toward rapid analysis of the locations of epileptic foci and the characterization of the temporal and spatial variations in epileptic discharges. This instrument is to be developed as a tool for clinical decision making. Further refinements of physical theory and the analysis of magnetic field maps will be tested by intraoperative cortical recordings.

SIGNIFICANCE: The potential of MEG to localize in three dimensions the source of neurologic discharges noninvasively offers a great advantage over conventional scalp EEG recording which suffers from the diffusion of scalp electrical potentials, due to high skull resistance. The localization of epileptic foci in patients inadequately responding to drug therapy is important in the evaluation of surgical prospects and the direction of surgical procedures. The noninvasive localization of coordinates of normal and abnormal neurologic activity in the brain offers the potential for much greater understanding of the topography of human brain neurologic processing.

PUBLICATIONS

Sato, S., and Smith, P.D.: Magnetoencephalography. *J. Clin. Neurophys.* 2 173-192, 1985.

Sato, S., Sheridan, P., Smith, P., Bonner, R., Weinstock, H., Nissenoff, M., Rose, D., Theodore, W., Friauf, W., and Porter, R.: Comparison of EEG, MEG and ECoG in epileptic patients. Biomagnetism: Applications and Theory. New York, Pergamon, 1984, pp. 311-315.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 RS 10170-03 BEI
PERIOD COVERED October 1, 1984 to September 30, 1985		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Biological Applications of a Computer Controlled Analytical Electron Microscope		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) R.D. Leapman Visiting Scientist BEIB, DRS		
Others: C.E. Fiori Physical Scientist BEIB, DRS C.R. Swyt Physical Scientist BEIB, DRS K.E. Gorlen Electronic Engineer CSL, DCRT C.C. Gibson Electronic Engineer BEIB, DCRT		
COOPERATING UNITS (if any) DCRT, NIADOK		
LAB/BRANCH Biomedical Engineering and Instrumentation Branch		
SECTION Electron Beam Imaging and Microspectroscopy Group		
INSTITUTE AND LOCATION DRS, National Institutes of Health, Bethesda, MD 20205		
TOTAL MAN-YEARS: 2.5	PROFESSIONAL: 2.5	OTHER:
CHECK APPROPRIATE BOX(ES) ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither ☐ (a1) Minors ☐ (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) Further advances have been made in the capabilities of the computer controlled analytical electron microscope, developed jointly by BEIB and DCRT, and the instrumentation has been applied to several biological problems in the past year. Two of these studies involved extensive electron energy loss spectroscopy. The newly installed Gatan 607 magnetic sector energy loss spectrometer has been shown to be fully corrected for second order aberrations. This has permitted a significant improvement in collection efficiency and energy resolution while allowing concurrent acquisition of energy dispersive x-ray (EDXS) and electron energy loss spectra (EELS) as well as simultaneous elastic dark field imaging in the scanning transmission mode. A basic study has been carried out to characterize the peak shapes of the x-ray detectors, and this has led to modifications to the Tracor Northern detector in order to improve performance. EELS and EDXS elemental maps and spectra have been obtained from pancreas beta cells prepared by rapid freezing, freeze-drying (or freeze-substitution) followed by embedding in order to investigate the composition of the secretory granules. Spectra have been quantitated to determine ratios of elements in the insulin-containing granule cores. A feasibility study has been made for obtaining low dose EELS maps using averaging procedures in periodic crystalline arrays of membranes. Data have been obtained from thin samples of reconstituted porin membrane containing lipid and protein sub-units and transmembrane channels. Both the experimental data and theoretical signal/noise estimations suggest that low dose elemental mapping should be possible.		

OTHER INVESTIGATORS

A. Boyne

Dept. Pharmacology and Experimental Therapeutics,
University of Maryland, Baltimore

A. Engel and R. Reichelt Biozentrum, University of Basel, Switzerland

OBJECTIVES: To determine how electron energy loss spectroscopy and energy dispersive x-ray spectroscopy can be optimized for biological research.

METHODS EMPLOYED: The Hitachi 200 keV analytical electron microscope operated under computer control has been developed further so EELS and EDXS spectroscopy and elemental mapping could be more optimally applied to biological problems. A new Catan 607 magnetic sector electron spectrometer has permitted simultaneous EELS, EDXS and dark field imaging to be carried-out for the first time.

MAJOR FINDINGS: Cores of insulin storage granules of beta cells from rat Islets of Langerhans showed N:S ratios that are consistent with N:S ratios obtained from pure commercial insulin crystals. Calcium and zinc were found both in the granules and in the commercial insulin. Moreover these elements were segregated into the granule rim in the beta cells whereas they were distributed homogeneously in the embedded insulin crystals. Electron energy loss spectra were recorded from large areas (10 square microns) of reconstituted E-coli porin membrane. Data obtained from unstained and sodium tungstate acid stained samples showed that phosphorus was detectable in the lipid component and nitrogen in the protein. A quantitative analysis agreed with the proposed model for the structure which consists of 3 porin polypeptides and 110 lipid molecules per unit cell (93 x 93 angstroms). It was estimated that the structure could be imaged with good signal/noise at a low dose (10 electrons per square angstrom) using a high resolution STEM probe if 10^4 unit cells were averaged.

SIGNIFICANCE: The results from the insulin storage granules demonstrate that quantitative EELS data can be obtained from rapidly frozen secretory cells. This could lead to a better understanding of the mechanisms for insulin storage and release in the pancreas beta cell. The apparent feasibility of low dose EELS phosphorus and nitrogen mapping in two dimensional membrane crystals is significant since it could provide a technique for localizing lipids and proteins in membranes without the limitations imposed by radiation damage.

PROPOSED COURSE: In the future it is planned to extend further the sensitivity of the EELS analysis by introducing a parallel multichannel detection system instead of the present serial detection system, thereby increasing the collection efficiency by a factor of 100 or 1000. Further data will be obtained from secretory cells including samples obtained by cryosectioning which preserves the distributions of diffusible ions. The application of low dose EELS mapping depends on the availability of a dedicated high resolution STEM.

Z01 RS 10170-03 BE1

PUBLICATIONS

- Leapman, R.D., Gorlen, K.E., and Swyt, C.R.: Processing of electron energy loss spectra and images. Scanning Electron Microscopy. 1: 1-13, 1985.
- Swyt, C.R. and Leapman, R.D.: Removal of plural scattering in electron energy loss spectra: practical considerations. In Romig, A.D. and Goldstein, J.I. (Eds.): Microbeam Analysis 1984. San Francisco Press, 1984, pp. 45-48.
- Leapman, R.D., Fiori, C.E., and Swyt, C.R.: Mass thickness determination by inelastic scattering in microanalysis of organic samples. In Williams, D.B. and Joy, D.C. (Eds): Analytical Electron Microscopy 1984. San Francisco Press, 1984, pp. 83-88.
- Leapman, R.D., Fiori, C.E., and Gorlen, K.E.: Elemental imaging by EELS and EDXS in the analytical electron microscope: its relevance to trace element research. Biol. Trace Element Res. (in press).
- Leapman, R.D. and Swyt, C.R.: Quantitative electron energy loss mapping. In Bailey, G.W. (Ed.): Proc. 43rd EMSA Conference. San Francisco Press, 1984, pp. 404-405.
- Boyne, A.F., Leapman, R.D., Wierwille, R. and Dudek, R.W.: Analytical electron microscopy of insulin storage granules. In Proc. Low Temperature Biological Microscopy Meeting, Royal Microscopical Society of Great Britain, 1985 (in press).

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 RS 10184-02 BEI												
PERIOD COVERED October 1, 1984 to September 30, 1985														
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Physical Chemistry of Biological Macromolecules														
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) Marc S. Lewis Research Chemist, BEIB/DRS <table style="width: 100%; border: none;"> <tr> <td style="width: 33%;">S.I. Chung</td> <td style="width: 33%;">Research Chemist</td> <td style="width: 33%;">LB NIDR</td> </tr> <tr> <td>G.W. Laurie</td> <td>Visiting Fellow</td> <td>LBDA NIDR</td> </tr> <tr> <td>G.R. Martin</td> <td>Laboratory Chief</td> <td>LBDA NIDR</td> </tr> <tr> <td>R.J. Youle</td> <td>Research Chemist</td> <td>SNB NINCDS</td> </tr> </table>			S.I. Chung	Research Chemist	LB NIDR	G.W. Laurie	Visiting Fellow	LBDA NIDR	G.R. Martin	Laboratory Chief	LBDA NIDR	R.J. Youle	Research Chemist	SNB NINCDS
S.I. Chung	Research Chemist	LB NIDR												
G.W. Laurie	Visiting Fellow	LBDA NIDR												
G.R. Martin	Laboratory Chief	LBDA NIDR												
R.J. Youle	Research Chemist	SNB NINCDS												
COOPERATING UNITS (if any) LB/NIDR, LBDA/NIDR, SNB/NINCDS														
LAB/BRANCH Biomedical Engineering and Instrumentation														
SECTION Microanalysis, O. Ch.														
INSTITUTE AND LOCATION DRS, National Institutes of Health, Bethesda, MD 20205														
TOTAL MAN-YEARS: 0.9	PROFESSIONAL: 0.9	OTHER:												
CHECK APPROPRIATE BOX(ES) ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither ☐ (a1) Minors ☐ (a2) Interviews														
SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.) The purpose of this project is to study the physical properties of a wide variety of biological macromolecules with the goal of correlating these properties to the structure and function of the macromolecules. The emphasis is on the thermodynamics of the interactions of these macromolecules and on their molecular size and shape. Analytical ultracentrifugation and mathematical modeling are the principal research techniques used. Studies on the association of fibrinogen with other proteins involved in blood clotting and fibrinolysis have been continued. Studies currently in progress in this area deal with the association of fibrinogen with plasma and platelet Factor XIII and with the association of plasminogen with the D and E fragments of fibrinogen. Studies on the association of the A and B chains of reduced ricin indicate that the formation of the AB complex is reversible and that the temperature dependence of this reaction indicates that it appears to be entropically driven, suggesting that there is a strong hydrophobic interaction between A and B chains even in the absence of the disulfide bond. Cell toxicity studies indicate that reduced ricin is more toxic than native ricin at high concentrations, indicating that the disulfide bond between the chains is not necessary for biological activity. The small and large forms of heparin sulfate proteoglycan isolated from EHS tumor basement membrane have been studied by electron microscopy and by analytical ultracentrifugation. These studies indicate that these proteoglycans show similarities in the number and size of the heparin sulfate side chains but differ in the length of the protein core.														

Z01 RS 10184-02 BEI

METHODS EMPLOYED: The macromolecules have been isolated and purified from appropriate sources by conventional methods. The associations have been studied by establishing equilibrium gradients in the analytical ultracentrifuge and then analyzing the resultant data by means of mathematical modeling techniques using the MLAB system operating on the DEC-10 computer.

MAJOR FINDINGS: **Proteins Involved in Blood Clotting:** Studies on the association of both plasma and Platelet Factor XIII with fibrinogen show that, like the association of plasminogen with this protein, there are four binding sites per fibrinogen molecule, that the binding is so highly cooperative that the presence of complexes of Factor XIII with fibrinogen involving the binding of fewer than four molecules of this protein per molecule of fibrinogen can not be effectively demonstrated, and that the total free energy change for the binding of the four moles of Factor XIII is -32 kcal per mole of fibrinogen.

Ricin: It was demonstrated that neither intact ricin nor the individual A and B chains which were isolated following cleavage of the disulfide bond by reduction exhibited any self-association. Exact equimolar mixtures of ricin A and B chains were prepared by reduction of the disulfide bond between them with beta-mercaptoethanol and reoxidation was prevented by the presence of dithiothreitol in the buffer solution. High pressure liquid chromatography demonstrated that the level of reoxidized or intact ricin was less than 1%. The use of exact equimolar mixtures permitted the application of the simplest form of mathematical modeling using the method of implicit constraints to govern the possible distributions of the A and B chains and the AB complex, which were found to be in reversible equilibrium. Determination of the natural logarithm of the equilibrium constant of this reaction as a function of temperature enabled calculation of the associated changes of enthalpy and entropy. Values of 14 kcal/mol/deg and 70 cal/mol/deg respectively were found for the changes of enthalpy and entropy of association of the A and B chains. The negative value of the free energy change of association indicates that the association reaction is entropically driven, suggesting the probability of strong hydrophobic interaction between the chains. Cell toxicity studies demonstrated that while reduced ricin is significantly less toxic than native ricin at very low concentrations, as its concentration is increased, its relative toxicity also increases, and it eventually becomes more toxic than native ricin. This clearly demonstrates that the presence of the disulfide bond between the A and B chains of ricin is not necessary for toxicity and also that the dissociability of the reduced ricin AB complex may actually have a toxicity enhancing effect.

Heparin Sulfate Proteoglycans: Small and large forms of heparin sulfate proteoglycan were isolated for EHS tumor basement membrane by sequential extraction. Electron microscopy demonstrated that these proteoglycans were present in an extended form on carbon film and that structures which could be interpreted as a protein core glycosaminoglycan side chains could be distinguished. The small proteoglycan had a 42 ± 25 nm long protein core with 4 to 6 25 ± 8 nm long side chains often grouped along one half of the core. A sedimentation coefficient of 2.9 S was found for the small proteoglycan and a sedimentation coefficient of 14.7 S was found for the large proteoglycan. Both large and small proteoglycans show similar numbers and sizes of side chain, differing principally in the size of the protein core. The much higher value for the sedimentation coefficient of the large proteoglycan would appear to be function of a marked tendency to undergo aggregation.

SIGNIFICANCE: The studies on the interactions of fibrinogen, and other proteins such as plasma and platelet Factor XIII are relevant to the very significant roles that these proteins play in blood clotting and subsequent fibrinolysis. It is our objective to correlate the physical chemistry of these interactions with the physiological role which these proteins play. The studies on ricin are relevant to an understanding of its structure and to its function as a toxin. Ricin appears to be formed as a single polypeptide chain which then undergoes cleavage followed by association of the A and B chains and then oxidation of two sulphydryls to form the disulfide bond; this study indicates how that association occurs. Bioassay studies on the toxicity of native and reduced ricin demonstrate that the disulfide bond is not necessary for toxicity and that there is a correlation between the degree of association of reduced ricin and its toxicity. The studies on the proteoglycans are the initial step in the study of the relationship of these structural elements with other proteins involved in basement membrane.

PROPOSED COURSE: A manuscript describing the studies on the binding of plasma and platelet Factor XIII by fibrinogen is in preparation at this time. More studies on the interactions of the proteins involved in blood clotting and subsequent fibrinolysis will be pursued extensively, as this appears to be a very fruitful area of endeavor.

A manuscript describing the ricin studies has been completed and will be submitted for publication. We plan to continue work in this area with studies on the association of ricin chains which have been coupled to cell-specific antibodies, with studies on other related A and B chain type toxins and with studies on the interaction of ricin with specific antibodies.

A manuscript on the heparin sulfate proteoglycans has been submitted for publication. We plan a study to quantify the polydispersity of these proteoglycans and then study their interaction with proteins such as laminin and type 4 collagen.

Studies on other A-B type associations are planned; preliminary studies on human chorionic gonadotropin appear particularly promising.

PUBLICATIONS

Redmond, T.M., Wiggert, B., Robey, F.A., Nguyen, N.Y., Lewis, M.S., Lee, L., and Chader, G.J.: Isolation and characterization of monkey interphotoreceptor retinoid-binding protein, a unique extracellular matrix component of the retina. Biochemistry 24: 787-793, 1985.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01RS 10185-02BEI
PERIOD COVERED October 1, 1984 to September 30, 1985		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Interventional Catheter Development		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) John W. Boretos, Physical Scientist, BEIB, DRS Others: John Doppman, M.D. Radiologist CR, CC, NIH Edward Oldfield, M.D. Neurosurgeon NINCDS, NIH Robert L. Dedrick, Ph.D. Chem. Engr. BEIB, DRS, NIH		
COOPERATING UNITS (if any) CR, CC, NIH; NS, NINCDS, NIH, BEIB, DRS, NIH		
LAB/BRANCH Biomedical Engineering and Instrumentation		
SECTION Chemical Engineering Section		
INSTITUTE AND LOCATION DRS, National Institutes of Health, Bethesda, MD 20205		
TOTAL MAN-YEARS: 1.4	PROFESSIONAL: 0.7	OTHER: 0.7
CHECK APPROPRIATE BOX(ES) ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither ☐ (a1) Minors ☐ (a2) Interviews		
SUMMARY OF WORK (Use standard unexpanded type. Do not exceed the space provided.) The purpose of the project is to develop a catheter system for interventional radiology which is capable of traversing small and branching blood vessels (i.e. 1.5 to 4.0 mm) to reach the proximity of tumors and to administer chemotherapeutic drugs to these tumors in a controlled manner. A major obstacle to effective treatment is thought to be maldistribution of the drug at the site due to inadequate mixing with the blood. A multi-lumen catheter, which is propelled and directed through these small blood vessels via jets of fluid emanating from its distal end, continues to show promise for negotiating heretofore difficult to reach areas. Fluid turbulence generated by drug emanating at retrograde angles from the tip of the catheter adds significantly to the mixing of the drug within the blood stream. Animal tests have substantiated the feasibility of the catheter system for clinical use. A transparent model of the vascular network simulating blood flow of a pulsatile nature was designed to evaluate the efficiency of the jet flow at various delivering rates. A high torque roller pump using custom designed polyurethane tubing is capable of producing satisfactory infusion rates over an 8 hour period.		

OBJECTIVES: The objective of this project is to develop a catheter system for interventional radiology which is capable of traversing small and branching blood vessels (i.e., 1.5 to 4.0 mm) to reach the proximity of cancerous tumors and to administer chemo-therapeutic drugs to these tumors in a controlled manner.

METHODS EMPLOYED: A multi-lumen microcatheter which is propelled and directed through small blood vessels via jets of fluid emanating from its distal end has shown promise for negotiating heretofore difficult to reach areas. The catheter is controlled by an adjustable pressurized manifold operated by foot switches. Radiopaque contrast solution is used to propel and visualize the movement of the catheter by being pumped selectively through the lumens of the catheter. As radiopaque fluid jets out of the catheter ports, thrust is transmitted to the tip of the catheter. Right, left, and forward motions can be controlled in this manner. The chemotherapeutic drug is brought on-line by valvular switching at the manifold to replace the contrast agent. The jet action of the fluid emanating at a retrograde angle from the tip of the catheter generates fluid turbulence which adds significantly to the mixing of the drug within the blood stream. A transparent model of the vascular network simulating pulsatile blood flow is being used to evaluate the efficiency of the jet catheter system and its behavior in administering chemotherapeutic drugs.

MAJOR FINDINGS: The multi-lumen catheter which is propelled and directed through small blood vessels via jets of fluid emanating from its distal end continues to show promise for negotiating heretofore difficult to reach areas of the vascular network. The jet propulsion action can be regulated to serve as a means of administering chemotherapeutic drugs. Because of its angular retrograde flow, mixing of the drug within the blood stream is significantly enhanced over that of an open ended catheter of a single orifice. Custom designed polyurethane tubing used with a high torque roller pump can provide constant perfusion of drug through the catheter systems at back pressures of 60 psi for up to 8 hours.

SIGNIFICANCE: Further development of the catheter system to increase fluid volumes under lower induced pressures along with characterization of the efficiency of intravascular drug administration. Clinical use is underway.

PUBLICATIONS

Lutz, R.H., Boretos, J.W., Dedrick, R.C., Oldfield, E.H., and Doppman, J.L.: Mixing studies during infusion into internal carotid artery model. Proc. AAMI, Boston 1985 p. 57.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 RS 10187-02 BEI
PERIOD COVERED October 1, 1983 to September 30, 1984		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Mixing During Intra-Arterial Infusion via Catheters		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)		
R. J. Lutz R. L. Dedrick B. Blacklock E. Oldfield, J. Doppman D. Miller	DRS, BEIB DRS, BEIB NINCDS, IR, SN NINCDS, IR, SN CC, DR CC, DR	J. Boretos C. Thompson R. Pflueger DRS BEIB DRS BEIB DRS BEIB
COOPERATING UNITS (if any) NINCDS CC		
LAB/BRANCH Biomedical Engineering and Instrumentation		
SECTION Chemical Engineering Section		
INSTITUTE AND LOCATION DRS, National Institutes of Health, Bethesda, MD 20205		
TOTAL MAN-YEARS: 1.5	PROFESSIONAL: 1.0	OTHER: .5
CHECK APPROPRIATE BOX(ES) ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither ☐ (a1) Minors ☐ (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) Intra-arterial chemotherapy offers an alternative to systemic (iv) chemotherapy for localized neoplasms. Infusion of chemotherapeutic agents directly into the arterial supply of the neoplasm allows, under proper circumstances, higher local tissue concentrations without a corresponding increase in systemic toxicity. Results using this treatment method in patients have varied. In some instances, cases of severe ophthalmic toxicity and of leukoencephalopathies have been reported. These findings suggested the possibility that streaming of the infused drug solution resulted in inadequate mixing and therefore non-uniform drug concentrations in the infused tissue region. Fluid-mechanical studies with an <u>in vitro</u> model of a human carotid artery system have demonstrated that streaming can occur at low infusion rates, and that mixing can be enhanced by increasing the infusion velocities and also by improving the design of the catheter tip, such as injecting transversely or retrograde to the artery flow. <u>In vivo</u> studies involving both slow and fast infusions of radiolabeled iodoantipyrine into the carotid artery of monkeys and subsequent autoradiographic analysis of brain slices have corroborated the findings of the <u>in vitro</u> model studies.		

OBJECTIVES: To assess the degree of mixing produced by infusion of solutions through several types of catheters at various injection velocities in an in vitro model of the carotid artery.

To measure the heterogeneity of radioactive tracer concentration in regions of the monkey brain after infusion at different rates into the internal carotid artery.

To determine methods for improving mixing during intra-arterial infusions.

METHODS EMPLOYED: A clear plastic model of the human internal carotid artery system and several major branches was fabricated by casting a resin (Alplex) around a low-melting alloy (Cerroloy) which was sculpted into a geometry determined from human angiographic photographs. The model was connected to a circulatory flow loop which produced steady or pulsatile flow. Still photographs, 16mm movie films, and video recordings were made of dye injections into a flowing blood simulant (40% glycerine/water) at several infusion rates at supraophthalmic and infraophthalmic catheter positions.

Fluid samples were also taken from the various branch arteries, and dye concentrations were analyzed spectrophotometrically to arrive at a quantitative measure of dye distribution proximal to the point of infusion. This data was represented in the form of histograms of branch dye concentration relative to a well mixed concentration for six branch collection sites; ophthalmic, choroidal, anterior cerebral, lenticulo-striates, and middle cerebrals.

A glass model of a portion of the human hepatic artery system has been fabricated. It, too, was modelled after a sequence of angiographic pictures in order to maintain a reasonably representative geometry. A separate flow system, similar to the carotid system, has been constructed and both qualitative photographic recordings and quantitative dye concentration measurements can be taken following infusion of dye or tracer into the gastroduodenal artery.

A series of in vivo experiments were performed in monkeys. The cervical segment of the carotid artery was exposed and the external carotid artery was ligated. Intracarotid infusions of ^{14}C -iodoantipyrine were done by direct puncture with a 30 gauge needle. Four monkeys received infusions at the rate of 0.4 ml/min (slow infusion group), and three monkeys received retrograde infusions at the rate of 4 ml/min to promote mixing (fast infusion group). The infusion lasted for 30 seconds at which time the brain was removed and frozen in liquid freon. The brain was thin sectioned on a sledge microtome and the tissue slices were autoradiographed to determine the distribution of radioactivity. The radioactivity data was digitized by a computerized scanning microdensitometer. The images were analyzed and examined for uniformity by comparing highest-to-lowest concentrations of radioactivity.

Z01 RS 10187-02

MAJOR FINDINGS: Streaming of dye solutions in the carotid model has been demonstrated to occur from several types of catheters when infusion velocities are slow relative to the surrounding fluid velocities. Mixing is enhanced by increasing the infusion rates. In general, at a given infusion rate, distribution of infusate at the distal branches is more uniform when catheters are placed in the infraophthalmic position. Catheters that eject infusate in a direction lateral or retrograde to the flowing solution appear to have better mixing properties than end hold catheters which eject in the direction of the flowing blood. When streaming conditions exist, concentrations in branches receiving streamers can be as high as three to five times the well-mixed value while some branches can receive no infusate at all. One such example of the high concentration was for the ophthalmic artery after a 2 ml/min infraophthalmic infusion.

Monkeys that received slow infusions of ^{14}C -iodoantipyrine showed very heterogenous distribution of tracer with high-to-low concentration ratios as great as 13 for regions in close proximity. For the fast infusion group, the high-to-low concentration ratio was approximately 1.5 and was not significantly different from a standard intravenous injection.

Preliminary results with the hepatic artery flow model indicate comparable results as those found with the carotid model.

SIGNIFICANCE: Inadequate mixing of drugs infused via intra-arterial catheters can result in variable drug exposure to distal tissue regions. Excessive drug exposure, particularly to sensitive normal tissue such as the eye, can result in unwanted toxic effects. Inadequate drug exposure can result in reduced therapeutic effect at a particular tumor site. With inadequate mixing, the exposure at all sites would be random and unpredictable.

PROPOSED COURSE: To continue to pursue an understanding of the fundamental fluid mechanical factors that affect mixing of jets in flowing fluids.

To study methods for enhancing mixing during intra-arterial infusions such as improved catheter tip design.

To continue experiments with the hepatic model and to quantitate the mixing characteristics of infusion into the gastroduodenal artery using the Infusaid pump.

To consider the effects of whole blood on the mixing of infusate in the carotid artery model.

PUBLICATIONS

Lutz, R.J., Boretos, J.W., Dedrick, R.L., Oldfield, E.H., and Doppman J.L.: Mixing studies during infusion into internal carotid artery model. Proc. 20th Ann. Mtg. Assoc. Adv. Med. Instrumentation, 1985, p.57.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 RS 10188-02 BEI									
PERIOD COVERED October 1, 1984 to September 30, 1985											
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Drug Transport in Brain											
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) <table style="width: 100%; border: none;"> <tr> <td style="width: 33%;">P.F. Morrison</td> <td style="width: 33%;">Physical Scientist</td> <td style="width: 33%;">BEIB, DRS</td> </tr> <tr> <td>R.L. Dedrick</td> <td>Chief, ChE Section</td> <td>BEIB, DRS</td> </tr> <tr> <td>E.H. Oldfield</td> <td>Neurosurgeon</td> <td>SN, NINCDS</td> </tr> </table>			P.F. Morrison	Physical Scientist	BEIB, DRS	R.L. Dedrick	Chief, ChE Section	BEIB, DRS	E.H. Oldfield	Neurosurgeon	SN, NINCDS
P.F. Morrison	Physical Scientist	BEIB, DRS									
R.L. Dedrick	Chief, ChE Section	BEIB, DRS									
E.H. Oldfield	Neurosurgeon	SN, NINCDS									
COOPERATING UNITS (if any) Surgical Neurology Branch, NINCDS											
LAB/BRANCH Biomedical Engineering and Instrumentation											
SECTION Chemical Engineering Section											
INSTITUTE AND LOCATION DRS, National Institutes of Health, Bethesda, MD 20205											
TOTAL MAN-YEARS 0.5	PROFESSIONAL: 0.5	OTHER:									
CHECK APPROPRIATE BOX(ES) ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither ☐ (a1) Minors ☐ (a2) Interviews											
SUMMARY OF WORK (Use standard unexpanded type. Do not exceed the space provided.) The transport and reaction of cisplatin in the brain of the rat has been investigated with the intent of refining estimates of associated parameters. These parameters are needed to prospectively model various tumor treatment modalities for expected efficacy. A steady-state reaction-diffusion model was capable of representing the total platinum concentration profiles in the cerebellum following a continuous 7-day infusion of drug. The infusate cannula was treated as a point source and flow of drug into CSF was shown to be negligible. Reaction of cisplatin with the sulfur-containing moieties of cells was examined in detail. Saturation of binding sites, primarily composed of cysteine, methionine, and some histidine residues, was found to occur within 1 mm of the cannula tip. Saturation was modeled approximately as the reaction of free cisplatin with the time-averaged unbound protein concentration. At distances far from the cannula, e.g. 4 mm, protein degradation products containing platinum begin to contribute to the total platinum profile but they were shown to account for only about 3% and no more than 20% of the total present. The best linear reaction rate of cisplatin with protein was found to be .005 .002 min⁻¹. Inclusion of convection effects near the cannula tip decreases this value, but by no more than 30%, while saturation effects tend to increase it by about 40%. The capillary permeability was found to equal 9.0x10⁻⁷ cm/sec and be nearly unaffected by saturation.											

Z01 RS 10188-02 BEI

OBJECTIVES: To determine the transport parameters and theoretical framework that describe the movement of drugs through brain tissue, thus providing a basis for the prospective evaluation of various treatment modalities.

METHODS EMPLOYED: Reaction-convection-diffusion equations applicable to brain tissue were formulated for several boundary and source conditions. The tissue was represented physically as a nearly homogeneous medium with capillaries and reaction sites evenly distributed throughout the tissue mass. Cisplatin was considered to be distributed over both its parent and mono-aquated species and to be fully mobile. It was lost from the tissue either by reaction with proteins or flow across capillary walls.

Approximate analytical methods were employed to investigate the significance of the saturability of binding sites and the production of Pt-containing degradation products due to protein turnover. Saturable reaction was treated approximately as the reaction of free cisplatin (whose profile is nearly time-independent due to its strong dependence on permeability and weak dependence on protein reaction) with the time-averaged unbound protein concentration. Time-averaging the binding concentration in this way led to a pseudo-steady-state diffusion equation for free cisplatin, and hence for total platinum. The breakdown of Pt-bearing protein to its degradation products was considered only for non-saturating conditions. In this case, the degradation species were considered to arise from a superposition of diffusion profiles originating from spherical shell sources of degrading protein.

MAJOR FINDINGS: Saturation of protein binding sites in brain tissue was found to occur in a region within 1 mm of the cannula tip following a 7-day infusion of 3 mM cisplatin at 0.9 $\mu\text{l/hr}$. Cisplatin-protein reaction rate constants derived from concentration profile data extending to 4 mm were thus only weakly affected by saturation, the linear constant increasing from .005 min^{-1} to .007 min^{-1} . Other analysis showed that convection effects, also confined to the first millimeter, tend to oppose saturation effects, decreasing the rate constant by no more than 30%. Permeability estimates are not affected by saturation. Final parameter values were: reaction rate, .005 min^{-1} to .007 min^{-1} ; capillary permeability, 9.0×10^{-7} cm/sec; diffusion constant, 1.9×10^{-6} cm^2/sec .

SIGNIFICANCE: Availability of transport parameters and knowledge of reaction effects now allows one to estimate the range of effective cisplatin concentrations within brain tissue when the tissue is dosed by flow across various brain surfaces.

PROPOSED COURSE: The modeling will be extended to the transport of cisplatin in tumor as well as normal tissue. It may also be extended to other agents such as Interleukin-2 transport and distribution in LAK therapy.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 RS 10191-02 HEI
PERIOD COVERED October 1, 1984 to September 30, 1985		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Continuous Optical Monitoring for Bacterial Cultures		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) G.M. Maxwell, Staff Fellow, BEIB, DRS S.B. Leighton, Senior Engineer, BEIB, DRS Ernst Freese, Chief, LMB, NINCDS		
COOPERATING UNITS (if any) LMB, NINCDS		
LAB/BRANCH Biomedical Engineering and Instrumentation Branch		
SECTION Mechanical Engineering Section,		
INSTITUTE AND LOCATION DRS, National Institutes of Health, Bethesda, MD 20205		
TOTAL MAN-YEARS: .25	PROFESSIONAL: .25	OTHER:
CHECK APPROPRIATE BOX(ES) ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither ☐ (a1) Minors ☐ (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) The incubation of bacterial cultures is a standard laboratory technique in numerous biological studies. Monitoring the growth of these cultures in a shaker bath or fermentor currently requires frequent manual sampling. The work on this project has been aimed at developing a system capable of continuously monitoring growth in situ using optical measurement techniques. To date the work has demonstrated the feasibility of making these measurements in shaker flasks employing an immersed detection system and yielded a prototype system for this application. Additional efforts have been directed at designing a system which will operate in a commercial type fermenter. The principal problem of eliminating gas bubbles in the optical path of the immersed probe has been solved.		

Z01 RS 10191-02 BEI

OBJECTIVES: The objectives of this project are twofold 1) To develop a system capable of continuously monitoring the growth of bacterial cultures in shaker flasks 2) To develop a system capable of maintaining a constant cell population in a fermenter.

METHODS EMPLOYED: A functional prototype for shaker flask monitoring has been developed and is in the final stages of testing. Testing is performed by monitoring a growing culture and comparing these results with measurements made by withdrawing samples and measuring their optical density in an absorption spectrophotometer. The withdrawal technique is a standard laboratory procedure.

An immersible detector capable of operating in the highly aerated environment of a commercial fermenter has been developed. Current testing is aimed at extending the length of time the probe can operate and at optimizing the control system needed to maintain a constant cell population density. An absorption spectrophotometer operating at 660 nm is used as the reference measurement of population density.

MAJOR FINDINGS: The prototype detector system for shaker flask measurements has been used to monitor the growth of Bacillus subtilis in a minimum mineral salts solution over an optical density range of 0 to 8 as measured at 660 nm by a standard absorption spectrophotometer. Readings may be taken as often as every 60 seconds without effecting the culture's growth rate (unmonitored growth is determined by standard measurements of an equal volume of culture in an equal volume flask.) and have an accuracy of 0.15 OD units over this full range.

SIGNIFICANCE: A shaker flask detection system with continuous monitoring has several advantages over manual sampling: 1) it is a labor saving device and as such frees the experimenter from taking manual samples, therefore permitting a larger number of cultures to be run simultaneously 2) it decreases the risk of contamination as the flask need not be opened for sample removal 3) it removes fluctuation in culture volume caused by manual sampling as a variable 4) it permits close monitoring of cell cultures with a rapid growth rate.

The fermenter control system would provide a simple method for performing long time course experiments under constant culture conditions and would aid in the harvesting of culture products.

PROPOSED COURSE Future work on the shaker flask detector will be directed toward design of a multi-channel system and toward evaluating the probe for use with yeast cultures. Future work on the fermenter probe will be directed at extending the useful life of the probe and towards optimization of the control system.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 RS 10193-02 BEI
PERIOD COVERED October 1, 1984 to September 30, 1985		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Development of Toposcopic Catheter for Clinical Gastroenterological Use		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) D.R. Shook, Biomedical Engineer. BEIB, DRS		
COOPERATING UNITS (if any) Naval Hospital Bethesda, Naval Medical Command, National Capital Region, USN (E.L. Cattau, T.J. Spurling); Esophageal, Gastric and Colonic Diseases, Digestive Diseases and Nutrition Division, NIADK (K.J. Vener).		
LAB/BRANCH Biomedical Engineering and Instrumentation Branch		
SECTION Mechanical Engineering Section,		
INSTITUTE AND LOCATION DRS, National Institutes of Health, Bethesda, MD 20205		
TOTAL MAN-YEARS: 0.3	PROFESSIONAL: 0.3	OTHER:
CHECK APPROPRIATE BOX(ES) ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither ☐ (a1) Minors ☐ (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) The unique characteristics of the toposcopic catheter have suggested its application in the gastrointestinal system. The operation of the catheter promises to facilitate the catheterization of the pancreatobiliary ducts through the Papilla of Vater. An initial series of patients has undergone routine endoscopic retrograde cholangiopancreatography (ERCP) using the topocatheter for contrast infusion. An extensively modified topocatheter is passed through an appropriately positioned endoscope. The catheter tip is placed within the ampulla, and the toposcopic element is everted. In basic ERCP, contract medium is then injected for appropriate diagnostic procedures. In addition, the topocatheter's ability to atraumatically negotiate small, tortuous ducts is being applied to catheterization of remote pancreatic and cystic ducts for sampling of pure secretions.		

Z01 RS 10193-02 BEI

OBJECTIVES: Develop techniques for selective toposcopic catheterization of small, tortuous ducts of the gastrointestinal system and optimize apparatus for varied diagnostic and therapeutic applications.

MAJOR FINDINGS: Experimental work has progressed sufficiently to justify catheterization of patients during routine ERCP procedures. A patient series has been started using a topocatheter modified for insertion and operation through a fiberoptic endoscope. The far reaches of the pancreatic duct have been safely catheterized and opacified at lower than conventional pressure. The five patient series has indicated that a more easily manipulated primary catheter material is required for convenient, full range ERCP techniques. The everting catheter is being adapted, therefore, by changing the primary catheter material to polytetrafluoroethylene (Teflon) and developing a technique to bond the polyurethane everting element to that material. Initial efforts have been encouraging, and another patient series for verification is anticipated.

SIGNIFICANCE: Catheterization of the far reaches of the pancreatic duct and branches coupled with sampling of pure secretions will reveal heretofore unavailable data on secretory activities as functions of digestion time and pathological state. Also of interest to clinical research is conveying fiberoptic probes for measuring chemical activity levels as near to the secretory source as possible. The topocatheter may greatly facilitate these applications without mechanical trauma and with much less risk of pancreatitis. The topocatheter has the potential to repeatedly and atraumatically negotiate the cystic duct for sampling of fluids and possible infusion of chemotherapy for dissolution of gall stones.

PROPOSED COURSE: Optimize catheter system for diverse clinical applications. Substantiate the use of the toposcopic concept in unique GI applications. Develop related devices and explore additional use for the catheter.

Related Project Number

Z01-RS-10-01 BEIB (Vascular use)

Z01-RS-10-01 BEIB (Polymer Processing)

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 RS 10194-02 BEI
PERIOD COVERED October 1, 1984 to September 30, 1985		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Optimized Polymer Processing for Advanced Catheter Development		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) D.R. Shook, Biomedical Engineer, BEIB, DRS B. Bourin, Guest Researcher, BEIB, DRS		
COOPERATING UNITS (If any) Diagnostic Radiology, CC (J.L. Doppman); Esophageal, Gastric and Colonic Diseases, Digestive Diseases and Nutrition Division, NIADKD (K.S. Vener)		
LAB/BRANCH Biomedical Engineering and Instrumentation Branch		
SECTION Mechanical Engineering Section,		
INSTITUTE AND LOCATION National Institutes of Health, Bethesda, MD 20205		
TOTAL MAN-YEARS: 0.6	PROFESSIONAL: 0.5	OTHER: 0.1
CHECK APPROPRIATE BOX(ES) ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither ☐ (a1) Minors ☐ (a2) Interviews		
SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.) Advanced techniques of plasticating extrusion can produce materials of optimized anisotropic properties and very fine dimensional characteristics. Availability of such materials then supports development of unique polymeric medical devices, such as the toposcopic catheter. Unique polymer resins are first characterized specifically for extrusion characteristics, and predictive models of rheological behavior are constructed. Die designs can now be implemented to take advantage of unique polymer character and to overcome the most critical processing difficulties. The models may also be used to eliminate certain polymers from consideration. Current efforts are to optimize the topocatheter material for maximally safe operation and to allow development of the topocatheter for arterial dilatation.		

Z01 RS 10194-02 BEI

OBJECTIVES: To produce advanced and state-of-the-art extrusions to allow development of unique catheter and general medical devices for diagnostic and therapeutic applications.

MAJOR FINDINGS: The processing system has been assembled and optimized for fine wall tubing extrusion. Major problems with the pressure and temperature control systems have been corrected. The rheological model of the topocatheter polyurethane is being developed. Phase I of that development, verification of the proposed model by analysis of a known material, is complete. Large time lags between temperature control and measurement and large swings in temperature caused lack of correlation between model and data. Therefore, an additional control zone is being added to the extruder to more closely control those variations.

SIGNIFICANCE: The availability of advanced materials processing technology is often the critical element in development of unique polymeric medical devices. The toposcopic catheter is an excellent example of a very useful device whose development was substantially delayed by lack of high quality processing capabilities. The economics of the medical device industry often restrict development efforts to known low-risk technologies. The present processing capabilities will permit and encourage the development of unique device designs that will reveal clinical and basic research applications not heretofore envisioned.

PROPOSED COURSE: To optimize topocatheter materials for maximum safety; to broaden topocatheter applications to arterial dilatation by customizing material anisotropies; to implement design modifications to allow convenient and reliable steering of the topocatheter.

RELATED PROJECT NUMBER

Z01-RS-10015-09-BEIB
Z01-RS-10-01 BEIB (GI use)

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 RS 10201-01 BEI
PERIOD COVERED October 1, 1984 to September 30, 1985		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Automated Cell Colony Scanner System		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) Dr. Seth Goldstein, Chief, Mechanical Engineering Section, BEIB, DRS Dr. Michael Brownstein, Chief, Laboratory of Cell Biology, NIMH		
COOPERATING UNITS (if any) Laboratory of Cell Biology, NIMH		
LAB/BRANCH Biomedical Engineering and Instrumentation		
SECTION Mechanical Engineering Section		
INSTITUTE AND LOCATION DRS, National Institutes of Health, Bethesda, MD 20205		
TOTAL MAN-YEARS: .65	PROFESSIONAL: .5	OTHER: .15
CHECK APPROPRIATE BOX(ES) ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither ☐ (a1) Minors ☐ (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) A system will be developed for the purpose of identifying, for subsequent cloning, a minute fraction of cells possessing a specific antibody or other fluorescent tag. Major emphasis will be put on making the system as simple and inexpensive and readily available to investigators as possible. A variety of concepts and techniques have been identified and evaluated, and the most promising will be developed into a computer controlled instrument.		

Z01 RS 10201-01 BEI

OBJECTIVES: To develop an inexpensive system to identify a minute fraction of cells having specific antibodies so they can subsequently be cloned.

SIGNIFICANCE: Many studies involving the "shotgun" approach to genetic engineering could be performed far more efficiently and easily if it were possible to identify the small percentage (e.g., $10^{-4}\%$) of cells that possess a particular antibody, using a relatively simple and inexpensive system. Whereas in principal, this is possible to do with a laser activated cell sorter, these devices are still quite expensive and are therefore not always readily available to investigators, and in some cases are not appropriate for a variety of reasons. It is anticipated that development of a system which overcomes these disadvantages should be of widespread interest to investigators using genetic engineering techniques and monoclonal antibodies.

PROPOSED COURSE: A variety of techniques will be explored, and the most promising will be selected. Different system configurations will be evaluated, and a prototype system will then be built and tested.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 RS 10202-01 BEI
PERIOD COVERED October 1, 1984 to September 30, 1985		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Optical Techniques for Dental Instrumentation		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) G.M. Maxwell, Senior Staff Fellow, BEIB, DRS R.L. Webber, Chief Diagnostic Systems Branch, CIB, NIDR		
COOPERATING UNITS (if any) CIB, NIDR		
LAB/BRANCH Biomedical Engineering and Instrumentation		
SECTION Mechanical Engineering Section		
INSTITUTE AND LOCATION DRS, National Institutes of Health, Bethesda, MD 20205		
TOTAL MAN-YEARS: .25	PROFESSIONAL: .25	OTHER:
CHECK APPROPRIATE BOX(ES) ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither ☐ (a1) Minors ☐ (a2) Interviews		
SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.) Two issues of importance in clinical dentistry are the assessment of a tooth's viability and the detection of caries in the regions where there is contact between adjacent teeth. Optical techniques are currently being explored as alternatives to present methods of measurement. Tooth viability is being examined by developing a system which can detect the presence of hemoglobin in the tooth by its absorption characteristics. The presence of caries between teeth is being assessed by measuring the fluorescence spectra which change with the development of tooth decay.		

Z01 RS 10202-01 BEI

OBJECTIVES: The purpose of this investigation is to explore the use of optical measurement techniques for routine clinical assessments in dentistry. Specifically two applications will be investigated: The detection of hemoglobin for evaluating tooth viability and the measurement of fluorescence for detecting caries.

METHODS EMPLOYED: An initial set of measurements was performed to determine whether small targets with known absorption spectra could be detected in excised teeth. Measurements are currently being conducted using freshly extracted teeth and the same teeth with all hemoglobin removed to evaluate the necessary device sensitivity and to gather preliminary population statistics to see whether normal and abnormal populations are sufficiently different to allow ready discrimination by these tests.

MAJOR FINDINGS: Preliminary measurements using one and three mm³ dyed targets with known spectra have demonstrated the possibility of detecting hemoglobin in teeth using a fiber optic system.

SIGNIFICANCE: In present clinical practice the evaluation of a tooth's viability is made by applying an electrical current to the tooth. Perception of this stimulation by the patient is used as a positive indication that the tooth is viable. It is not always clear, however, that the perception is caused by the stimulation of the nerve within the tooth. Stimulation of nerve fibers in adjacent teeth or the surrounding tissue can lead to a false positive. Additionally loss of neural irritability may occur without loss of circulation and thus produce a false negative. Successful development of an optical system which directly measures hemoglobin content will provide an independent measure of tooth viability which is specifically dependent on the parameter of interest i.e. internal perfusion of the tooth.

PROPOSED COURSE: After initial studies have defined the sensitivity and spectral bands necessary for detection of hemoglobin, a prototype system will be constructed and employed in clinical trials to evaluate the effectiveness of the method in determining tooth viability.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 RS 10203-01 BEI
PERIOD COVERED October 1, 1984 to September 30, 1985		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Clinical Assessment of Arterial Mechanical Properties		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) G.M. Maxwell, Senior Staff Fellow, BEIB, DRS R. Chadwick, Biomedical Engineer, BEIB, DRS D. Goldstein, Senior Investigator, IR, HE, NHLBI		
COOPERATING UNITS (if any) IR HE, NHLBI		
LAB/BRANCH Biomedical Engineering and Instrumentation		
SECTION Mechanical Engineering Section		
INSTITUTE AND LOCATION DRS, National Institutes of Health, Bethesda, MD 20205		
TOTAL MAN-YEARS: .25	PROFESSIONAL: .25	OTHER:
CHECK APPROPRIATE BOX(ES) ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither ☐ (a1) Minors ☐ (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) The purpose of this research is to develop an appropriate instrumentation system and associated data analysis techniques for evaluating the in-vivo mechanical properties of the brachial artery. Of particular interest is arterial distensibility, which can be evaluated in several ways. The most straightforward technique involves simultaneous measurement of arterial pressure and vessel diameter. An indirect and qualitative approach is also possible by analysis of the velocity waveform, a technique which can be performed non-invasively. Additionally, there are several theoretical formulations for arterial distensibility. Work on this project will be directed towards evaluating these various techniques to determine the limitations and advantages of each and to develop an instrumentation system suitable for routine clinical assessment of arterial mechanical properties.		

Z01 RS 10203-01 BEI

OBJECTIVES: It is the goal of this project to develop the necessary instrumentation and data analysis techniques to clinically evaluate the mechanical properties of the brachial and/or radial artery.

MAJOR FINDINGS: The measurement of distensibility has been made in three ways. The first method computes distensibility from measurements made with an internal pressure transducer and diameter measurement made with an ultrasonic echo tracking system. Because it would be desirable from a clinical standpoint to have a non-invasive technique, the second and third methods employ an indirect determination of the pressure gradient. One method measures the distensibility at two points and the other the velocity at two points. The distensibility is a function of the difference of these two measurements.

Both indirect methods have been determined to lack sufficient resolution to make a difference measurement feasible. Consequently only the invasive technique is considered to be a viable approach at this time.

SIGNIFICANCE: Results from the direct measurement of distensibility will permit the verification of theoretical predictions of the relationship between arterial mechanics and hypertension. Development of a non-invasive velocity system will permit the routine clinical evaluation of these properties and the effects of various therapies on the treatment of hypertension.

PROPOSED COURSE: Future efforts will be directed at constructing an appropriate fixation system for the arm and attendant fixturing for the transducers in order to make clinical measurements. The transducers will be interfaced to a computer system for performing the data collection and spectral analysis. Synchronization of data collection to the subjects EKG will be used to permit signal averaging in the frequency domain for noise reduction. A second approach to characterization of the mechanical properties will be pursued based on analysis of velocity waveforms. This technique will be qualitative but non-invasive and will proceed from an analysis of the velocity waveform in both the time and frequency domain to develop an extraction routine sensitive to changes in the mechanical properties of the artery. Clinical use of the resultant instrumentation system will involve determining how changes in the mechanical response of the artery are related to hypertension and associated drug therapies.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 RS 10204-01 BEI

PERIOD COVERED

October 1, 1984 to September 30, 1985

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Cell Handling Studies

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

S.B. Leighton, Mechanical Engineer, BEIB, DRS

J.A. Berzofsky M.D., DCBD, NCI

COOPERATING UNITS (if any)

DCBD, NCI

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Mechanical Engineering Section

INSTITUTE AND LOCATION

DRS, National Institutes of Health, Bethesda, MD 20205

TOTAL MAN-YEARS:

.2

PROFESSIONAL:

.2

OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects

☐ (b) Human tissues

☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use stencil if unreduced type. Do not exceed the space provided.)

It is desirable to handle and process individual cells for monoclonal antibody work and other research endeavors. We are investigating a number of modalities for this, including flow cytometry, micromanipulators, dielectrophoresis, micropipettes, microtitre trays, and tissue culture techniques. We are considering sorting, storing, transporting and selectively inactivating cells. In addition, we are considering magnetic, gradient density, antigen-antibody, and solubility difference methods as possible candidates for separation techniques.

Z01 RS 10204-01 BEI

OBJECTIVES: To provide a means of identifying and handling cells chosen by suitable criteria for successive stages of monoclonal antibody work.

METHODS EMPLOYED: The literature has been searched to familiarize ourselves with the current state of the art. The techniques listed above have been identified as worth further study. Advantages and disadvantages of these techniques are catalogued.

MAJOR FINDINGS: There are as yet no major findings, as this work is still in the preliminary stages.

SIGNIFICANCE: This work, if successful, could lead to improving the yield of monoclonal antibody derivations.

PROPOSED COURSE: Less promising techniques will be eliminated from consideration, and the most promising ones will be further refined into preliminary designs for evaluation.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 RS 10205-01 BEI
PERIOD COVERED October 1, 1984 to September 30, 1985		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Constant Shear Field Apparatus for ESR Studies		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) S.B. Leighton, Mechanical Engineer, BEIB, DRS H. Kon, Reserach Chemist, LCP, NIADOK		
COOPERATING UNITS (If any) LCP, NIADOK		
LAB/BRANCH Biomedical Engineering and Instrumentation		
SECTION Mechanical Engineering Section		
INSTITUTE AND LOCATION DRS, National Institutes of Health, Bethesda, MD 20205		
TOTAL MAN-YEARS: .2	PROFESSIONAL: .1	OTHER: .1
CHECK APPROPRIATE BOX(ES) ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither ☐ (a1) Minors ☐ (a2) Interviews		
SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.) Electron Spin Resonance (ESR) is a valuable technique for studying membrane bound proteins. In particular, it can be used to study labeled proteins in red blood cell membranes. In order to know the orientations of the proteins with respect to the membranes, it is necessary to orient the membranes with respect to the ESR device. A fluid shear field serves the purpose of orientation, since the red blood cells are discoid and distensible. However, flow in capillary tubes, although functional and simple, provides a non-uniform shear field due to the Poiseuille velocity distribution. We are planning to use a moving thin polyester tape to create a uniform shear field and hence sharper resolution of orientation and a better signal to noise ratio.		

Z01 RS 10205-01 BEI

OBJECTIVES: To provide a uniform shear field in a small sample of erythrocyte or other suspension, compatible with the D.C. magnetic and R.F. magnetic and electrical fields of the ESR apparatus, and to have a precisely controlled shear field.

METHODS EMPLOYED: A machineable ceramic, quartz, and glass housing will be constructed to fit within the 11 mm. diameter x 25 mm. long microwave cavity of the ESR instrument. This housing will hold the sample suspension and will provide precise guides for a mylar tape that will pass through the housing, turn 180 degrees and travel simultaneously past itself in the opposite direction. Three regions will be formed, bounded by the walls of the housing and the two sections of tape. Shear will be constant, determined by the spacings in the device and the speed of the tape.

MAJOR FINDINGS: The preliminary design of the apparatus is complete, and no theoretical obstacles to its successful completion have been discovered.

SIGNIFICANCE: This device, when complete, should allow ESR investigators better resolution in their measurements.

PROPOSED COURSE: The final design will be completed, and the instrument will be built and tested. The shear field will be examined by observing the alignment of the erythrocytes microscopically, through observation ports planned for that purpose. A computer interface for control of the experiment is planned.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE		PROJECT NUMBER
NOTICE OF INTRAMURAL RESEARCH PROJECT		Z01 RS 10206-01 BEI
PERIOD COVERED January 1, 1984 to September 30, 1985		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Concentration Uniformity by Diastolic Phasing of Pulsed Intra-Arterial Infusions		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) D.R. Shook, Biomedical Engineer, BEIB, DRS J.L. Doppman, Chief, DRD, CC		
COOPERATING UNITS (If any) Diagnostic Radiology, CC (J.L. Doppman, M. Girton); Chemical Engineering Section, BEIB, DRS (R.J. Lutz, R.L. Dedrick)		
LAB/BRANCH Biomedical Engineering and Instrumentation		
SECTION Mechanical Engineering Section		
INSTITUTE AND LOCATION DRS, National Institutes of Health, Bethesda, MD 20205		
TOTAL MAN-YEARS: 0.3	PROFESSIONAL: 0.3	OTHER:
CHECK APPROPRIATE BOX(ES) ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither ☐ (a1) Minors ☐ (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) Inadequate infusate/blood mixing during intra-arterial chemotherapy at low catheter infusion rates (1 ml/min) produces highly nonuniform downstream drug concentrations. Inadequate treatment of the lesion and overexposure of normal tissues may result. Studies are underway to investigate the advantage of diastolically phased, high flow rate, pulsed intra-arterial infusions in effecting uniform downstream concentrations. Triggered by the ECG, a high velocity pulse during the interval of lowest blood velocity and retriggered on successive cardiac cycles, will yield average flow rates at the desired therapeutic value. Apparatus to produce that pulsed flow and methods of <u>in vivo</u> evaluation of downstream concentration uniformity are being developed. <u>Highly realistic flow studies in an accurate model of the superior carotid artery and cerebral branches have demonstrated essentially complete concentration uniformity as determined by spectrophotometric comparison of infusate dye concentrations in all downstream branches. Upon optimization of the apparatus for animal and clinical use, and determination of appropriate clinical evaluation methods, pulsed intra-arterial infusions will be used in low flow rate clinical chemotherapeutic treatments.</u>		

Z01 RS 10206-01 BEI

OBJECTIVES: Evaluate effectiveness of diastolically phased, pulse intra-arterial infusions in attaining uniform downstream drug concentrations in chemotherapy.

MAJOR FINDINGS: Early in vitro studies indicate complete mixing and concentration uniformity due to pulsed intra-arterial infusions phased during the interval of lowest circumfluent blood velocity. Studies were conducted in realistic vascular model of the superior internal carotid artery and major branches by spectrophotometrically evaluating dye concentration in branch arteries.

SIGNIFICANCE: The possibility of streaming during intra-arterial chemotherapeutic infusions has been recognized. Low catheter infusion rates (1 ml/min) do not disturb the laminar nature of the blood flow and therefore allow the infusate to follow a restricted set of laminae. As downstream branches in the vasculature divide the flow, this restricted set of laminae may remain undivided and flow in toto into a side branch, sparing the intended vessel and downstream lesion of effective therapy. At best, the downstream drug concentrations are markedly nonuniform. By exploiting the inherent mixing of high flow rate infusions (high relative velocities) with the circumfluent blood flow, complete uniformity can be achieved. Average flow rates in the therapeutic range (desired administration schedules) are maintained by catheter delivery of these short, high velocity pulses of infusate during the interval of lowest blood flow within successive cardiac cycles, and triggered by the ECG.

PROPOSED COURSE: The apparatus will be optimized for animal use and a method to evaluate in vivo concentration uniformity determined. Animal studies will then be used to adapt the design for effective chemotherapy in the clinical setting.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 RS 10207-01 BEI
PERIOD COVERED October 1, 1984 to September 30, 1985		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Clinical Engineering Program for Hospital Patient Care Areas		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) R. Corsey, Electronic Engineer, ACES, BEIB		
COOPERATING UNITS (if any) OD CC		
LAB/BRANCH Biomedical Engineering and Instrumentation		
SECTION Applied Clinical Engineering		
INSTITUTE AND LOCATION DRS, National Institutes of Health, Bethesda, MD 20205		
TOTAL MAN-YEARS: 0.5	PROFESSIONAL: 0.5	OTHER:
CHECK APPROPRIATE BOX(ES) ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither ☐ (a1) Minors ☐ (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) This program has evolved from the Electrical Safety Program for patient care areas. It is designed to provide preventative maintenance for patient care equipment, electrical safety testing for equipment both clinical and research in nature, and electrical safety for patient care areas. Auxiliary services provided include incident investigation for equipment failure and misadventures, and education of medical and support personnel regarding equipment hazards and guidance for utilization of electronic technology in patient care. In addition this program assures hospital compliance with patient care electrical standards of the Joint Commission on Accreditation of Hospitals and the Health Care Facilities section of the National Electric Code.		

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 RS 10208-01 BEI
PERIOD COVERED October 1, 1984 to September 30, 1985		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Hemodynamic Principles in the Control of Coronary Blood Flow		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) Thomas L. Talbot, MS, ACES, BEIB Stephen E. Epstein, M.D. Cardiology, NHLBI Richard O. Cannon, III, M.D. Cardiology, NHLBI		
COOPERATING UNITS (if any) Cardiology Branch, NHLBI		
LAB/BRANCH Biomedical Engineering and Instrumentation		
SECTION Applied Clinical Engineering		
INSTITUTE AND LOCATION DRS, National Institutes of Health, Bethesda, MD 20205		
TOTAL MAN-YEARS: 1.5	PROFESSIONAL: 1.5	OTHER:
CHECK APPROPRIATE BOX(ES) ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither ☐ (a1) Minors ☐ (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) The effects of atherosclerotic epicardial stenosis on coronary vascular resistance can be understood in terms of basic fluid mechanical principles. Resistance is directly related to the trans-stenotic pressure drop and inversely related to flow. However, even with a fixed anatomic stenosis, resistance is not fixed; it increases as trans-stenotic flow increases. This exacerbates the <u>pressure drop across the stenosis</u> that develops as a result of flow; at high flows, large pressure drops can occur. This characteristic of flow through stenotic lesions can contribute to a "steal" physiology, between either epicardial or intramural coronary arteries. Studies have also shown the clinical importance and influence of <u>dynamic alterations in coronary resistance</u>, occurring either at the large or small vessel level. In addition, compressive forces exerted by the myocardium or by elevated intraventricular pressures can increase coronary vascular resistance, and therefore can interfere with myocardial perfusion. All these factors must be considered in order to understand the mechanisms leading to myocardial ischemia, and therefore to the clinical syndrome of <u>angina pectoris</u>.		

Z01 RS 10208-01 BEI

OBJECTIVE: Increase the clinician's understanding of the physics involved in the restriction of blood flow in order to promote a more in-depth understanding of the physiology of certain coronary disorders.

METHODS EMPLOYED: Mathematical treatment of simple restrictions in vessels as simple luminal narrowings in rigid tubes. Present results of calculation graphically and simply at first and subsequently increasing the complexity of the governing equations to encompass second and third order effects. Experimental data from dogs will serve as tests of hypotheses reached from the mathematical calculations.

SIGNIFICANCE Often myocardial ischemia occurs when the classical evidence of vasoconstriction would not indicate a severe decrease in coronary blood flow. A more thorough understanding of the factors that effect coronary blood flow will provide the clinician with a better ability to detect and treat potential ischemic conditions.

PROPOSED COURSE: To begin with simple first order calculation and measurements in models and eventually expand theory and experiments to predict and measure more detailed flow characteristic in the coronary arteries.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 RS 10209-01 BEI

PERIOD COVERED

October 1, 1984 to September 30, 1985

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Evaluation of Disposable Blood Pressure Transducers

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

E.C. Walker, Mechanical Engineer, ACES, BEIB

T.L. Talbot, Mechanical Engineer, ACES, BEIB

R.E. Clark M.D. Chief, Heart Surgery, NHLBI

D. Lawson, M.D.

COOPERATING UNITS (if any)

NHLBI, Heart Surgery

CC, ICU

CC, Anesthesiology

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Applied Clinical Engineering

INSTITUTE AND LOCATION

DRS, National Institutes of Health, Bethesda, MD 20205

TOTAL MAN-YEARS:

2

PROFESSIONAL:

1.7

OTHER:

0.3

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects☐ (b) Human tissues☐ (c) Neither☐ (a1) Minors☐ (a2) Interviews

SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.)

A sample of each manufacturer of disposable blood pressure transducers was tested for compliance to AAMI's specifications for these devices. The data are currently being compiled for presentation to those responsible for placing these devices in use throughout the Clinical Center. The data does not represent an official endorsement of a particular device.

OBJECTIVE: To define the best disposable transducer(s) for use in the various intramural applications.

METHODS The transducers are tested in a temperature and humidity controlled chamber. All specifications for such devices are tested using standard industrial testing techniques. All data is taken with the aid of a small computer for storage and subsequent analysis.

SIGNIFICANCE: Due to the burgeoning types of disposable pressure transducers, careful consideration of specification and reliability of quoted specification must be made before safely introducing a device into the varied areas throughout the Clinical Center.

PROPOSED COURSE: Ten of each manufacturer's disposable transducers will continue to be tested for compliance to AAMI specifications. These tests include defibrillation isolation and tolerance, frequency response, linearity, drift, sensitivity and light sensitivity. In addition other observations will be noted from an engineering and an end user perspective such as ease of debubbling, ease of application, out of box failure and ease of operation.

PUBLICATIONS

Walker, E.C., Talbot, T.L., Seipp, H.W., Sweeney, W.V., Dolan, D.P., and Clark, R.F.: A preliminary assessment of disposable blood pressure transducers. Advances in Bioengineering, Dec. 1984.

Walker, E.C., Lawson, D., Talbot, T.L., and Dolan, D.P.: An engineering evaluation of disposable resistive bridge type blood pressure transducers, Proceedings AAMI 20th Annual Meeting, May 1985.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 RS 10210-01 BEI
PERIOD COVERED May 4, 1984 to June 10, 1985		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Electronic Patient Monitoring		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) H.E. Cascio, Electronic Engineer, BEIB, DRS R. Corsey, Electronic Engineer, BEIB, DRS D. Cirelli, Administrator Officer, CC, OD K. Musallam, Nurse, CCNURS		
COOPERATING UNITS (if any) CCOD		
LAB/BRANCH Biomedical Engineering and Instrumentation		
SECTION EEES and ACE		
INSTITUTE AND LOCATION DRS, National Institutes of Health, Bethesda, MD 20205		
TOTAL MAN-YEARS: 0.4	PROFESSIONAL: 0.2	OTHER: 0.2
CHECK APPROPRIATE BOX(ES) ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither ☐ (a1) Minors ☐ (a2) Interviews		
SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.) An electronic patient monitoring system that would alert the nursing staff when a patient (or patients) is leaving the nursing unit would be a welcome aid in the care of Alzheimer's disease patients. The system design is based on a wrist watch size radio transmitter, worn by the patient, with each transmitter having a different modulating frequency. A detector unit, placed at the two exit locations, would sense the presence of any patients in these exit areas. The detection of a patient's transmitter would activate an alarm at the nurses' station and would also generate a display giving the area and the name of the exiting patient. This system would be built for the 12 E Aging PCU but would also be of use for other units having similar needs.		

OBJECTIVES: To design and fabricate a system to alert the nursing staff when one of their Alzheimer's disease patients is leaving the nursing area.

METHODS EMPLOYED: A miniaturized battery powered radio transmitter will be constructed in a plastic watch case. The transmitter, worn by the patient, will have a broadcast range of six feet. Each transmitter will have a different modulation frequency so that each patient can be identified. The two doors leading out of the nursing unit would be monitored by placing a modified broadcast radio at each door. The carrier frequency of all the transmitters will be the same (just above the broadcast band). The detected signals from the patients' transmitters are fed to a comb filter, which determines the transmitters that are being sensed. By means of a microprocessor controller, an alarm would be activated and the names of the patients and their location would be displayed on the nurses' display panel. A scheme to activate a door lock when a patient enters the sensing area is being studied. This function would not be implemented unless the monitoring system is allowed to be interfaced to the Clinical Center fire alarm signal system, which unlocks all doors in case of a fire.

SIGNIFICANCE: The task of keeping the confused Alzheimer's disease patients from becoming lost in the Clinical Center would greatly aid the nurses and increase the personal safety of the patients.

PROPOSED COURSE: A prototype breadboard has been constructed and demonstrated. The demonstration proved the feasibility of the design concept. The miniature radio transmitter will be fabricated and tested for reliability. The system electronics will be fabricated and installed on the 12 E nursing unit. The system will be initially tested with four patient transmitters with plans for the system to accommodate sixteen patient transmitters.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 RS 10211-01 BEI
PERIOD COVERED October 1, 1983 to September 30, 1984		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) IEEE-488 GPIB and Personal Computer Instrumentation Use Program Development		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) T.R. Clem, Sr., Electronic Engineer, EEES, BEIB, DRS		
COOPERATING UNITS (if any)		
LAB/BRANCH Biomedical Engineering and Instrumentation Branch		
SECTION Electrical and Electronic Engineering Section		
INSTITUTE AND LOCATION DRS, National Institutes of Health, Bethesda, MD 20205		
TOTAL MAN-YEARS: 0.25	PROFESSIONAL: 0.2	OTHER: 0.05
CHECK APPROPRIATE BOX(ES) ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither ☐ (a1) Minors ☐ (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) The increased availability and reduced cost of the small <u>Personal Computer</u> has created increased interest in <u>automating data acquisition</u> and process or experiment control in areas where such things were not feasible before due to cost or complexity. With these changes also came a significant increase in the use of the <u>IEEE-488 GPIB</u> by instrument makers. By combining the two, sophisticated instrumentation and data acquisition systems can be assembled quickly and inexpensively. The BEIB is continuing to develop the expertise to provide guidance and assistance to requirements where this approach provides the optimum solution. This capability is further assisted by the BEIB-SERP specifying the IEEE-488 interface on new equipment acquisitions whenever possible. The increase at the NIH in the numbers and use of the IBM PC has made this capability of great value to the NIH Intramural Research program.		

OBJECTIVE: Continue to develop expertise in the Branch in the use of IEEE-488 GPIB equipment, instruments, and controllers and recommend bus-compatible instruments for acquisitions by the SERP in order to be prepared to respond quickly to requests for an instrumentation systems.

METHODS EMPLOYED: Generally an instrumentation system will be assembled around the IEEE-488 GPIB for one of four reasons: 1) a prototype system is desired to prove feasibility before a dedicated system is designed and built, 2) a temporary system is needed to satisfy an urgent, short term need, such as replacing a dedicated system that is out of operation for maintenance or repair purposes, 3) to expedite data acquisition into a computer system for further analysis, or 4) to produce a system which is inherently flexible enough to adapt to a wide range of potential future needs.

SIGNIFICANCE: The capability of assembling an instrumentation system with a controller and GPIB-controlled instruments allows the EEES to provide a rapid response to an investigator's call for instrumentation. By assembling a system with "off-the-shelf" instruments from the SERP, the cost of special-purpose measurement or control systems can be kept quite low. If the experiment is a short-term project the instruments can be returned to the SERP with virtually no expenditures, by the investigator, for equipment.

PROPOSED COURSE: Continue to maintain state-of-the-art capability in the field of bus-compatible instruments and controllers. Seek to make this capability better known and understood around NIH. Expand capability which includes IBM PC's as controllers, and integrating systems with other types of PC-based I/O hardware. Develop expertise in assembling instrumentation systems using PC's and commercially - available laboratory acquisition and analysis programs.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 RS 10212-01 BEI
PERIOD COVERED October 1, 1984 to September 30, 1985		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Fluoroimmunoassay Apparatus		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) W.S. Friauf Ch., EEES BEIB, DRS R.L. Berger Physicist LTD NHLBI G. Hemphill Electronic Tech. BEIB, DRS		
COOPERATING UNITS (if any) CDC, Atlanta		
LAB/BRANCH Biomedical Engineering and Instrumentation Branch		
SECTION Electrical and Electronic Engineering Section		
INSTITUTE AND LOCATION DRS, National Institutes of Health, Bethesda, MD 20205		
TOTAL MAN-YEARS: 0.4	PROFESSIONAL: 0.3	OTHER: 0.1
CHECK APPROPRIATE BOX(ES) ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither ☐ (a1) Minors ☐ (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) New rare earth chelate fluorescent probes with a decay time constant much longer than the background decay time-constant of typical organic materials offer the potential of a great improvement in sensitivity by appropriate timing of the response. However, to rival radioimmunoassay methods the required sensitivity improvement is so great that overload recovery of the fluorescence detector is a major problem. Extensive past work on this problem is largely inapplicable to the very low speed and level requirements of this situation. Consequently initial effort is being applied to determining the optimum fluorescence detection device and ancillary signal overload limiting circuitry. Problems related to the fluorescent probe at extremely low sample concentrations will be studied in collaboration with CDC, which is interested in this approach as another tool for AIDS research. Finally an evaluation of the details of excitation, optical filtering, and digital signal processing will be worked out and optimized.		

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 RS 10213-01 BEI
PERIOD COVERED October 1, 1984 to September 30, 1985		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Vitreous Fluorophotometry Analysis		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
P.M. Bungay	Chemical Engineer	BEIB, DRS
K.F. Bonner	Biophysicist	BEIB, DRS
M.S. Roy	Ophthalmologist	CB, NEI
M.J. Podgor	Statistician	BE, NEI
COOPERATING UNITS (if any) Clinical Branch, NEI; Office of Biometry & Epidemiology, NEI		
LAB/BRANCH Biomedical Engineering and Instrumentation		
SECTION Chemical Engineering Section		
INSTITUTE AND LOCATION DRS, National Institutes of Health, Bethesda, MD 20205		
TOTAL MAN-YEARS: 1.0	PROFESSIONAL: 1.0	OTHER:
CHECK APPROPRIATE BOX(ES) ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither ☐ (a1) Minors ☐ (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) <u>Vitreous fluorophotometry (VFP)</u> is a clinical procedure for measuring the spatial distribution of fluorescence along the optical axis in a human subject's vitreous following administration of a fluorescent dye. In this project the clinical instrument is a Fluorotron Master manufactured by Coherent, Palo Alto, CA, and the dye is sodium fluorescein given by intravenous injection. The purpose of the project is to improve the protocols for conducting the measurements, processing the output from the instrument and analyzing the results from the population of normal volunteers and patients. One disease to be considered is <u>diabetes</u> and the associated pathology <u>diabetic retinopathy</u>. The goals are to evaluate the procedure for use in (1) <u>screening for early detection</u>, and (2) <u>monitoring for treatment efficacy</u>. A <u>pharmacokinetic mathematical model</u> has been developed which describes the rate of appearance of fluorescein in the vitreous in terms of the <u>blood-retinal barrier permeability</u> (characterized by <u>permeability coefficients</u> of the retina-vitreous interface) and transport of fluorescein within the vitreous by diffusion (characterized by a <u>diffusion coefficient</u>). <u>Plasma protein binding</u> of fluorescein is also incorporated. Measurements have been made on 22 normal volunteers to evaluate the performance of the instrument, establish baseline parameter ranges, and critique existing protocols/analysis schemes.		

Z01 RS 10213-01 BEI

OBJECTIVES: The objective is to evaluate vitreous fluorophotometry through improving the protocols for conducting measurements, processing the instrument output and analyzing the results from patient populations and normal controls. The intent is to extend the evaluation in the direction of discerning the procedure's usefulness in (1) screening for early detection of retinopathy and/or (2) monitoring the effectiveness of treatment in slowing the progression or reversing the development of blood-retinal barrier alterations.

METHODS EMPLOYED: A Fluorotron Master, manufactured by Coherent, Palo Alto, CA, is being used in the evaluation. This instrument was designed for clinical use. However, judging from the variety of protocols that have been proposed, the developers had not optimized the procedures and there is considerable skepticism in the research community about the instrument. Consequently it was deemed necessary to perform existing procedures on a population of normal volunteers coupled with the development of mathematical model to understand the normal in vivo phenomena involved, as well as the response characteristics of the instrument.

The existing procedures involve the single bolus injection of sodium fluorescein into an antecubital vein at a dose of 14 mg/kg. Blood samples are withdrawn from the contralateral vein at four time points over the succeeding 90 minutes in order to measure the decay of plasma levels of fluorescein and the variation over time in the percent of fluorescein binding to plasma proteins. The instrument is used to measure the spatial distribution of fluorescence within each eye at four time points: before fluorescein injection and nominally at 3, 30 and 60 minutes post-injection. The instrument illuminates the interior of the eye with a narrow, off-axis beam of monochromatic light and detects emitted light rays which follow a similar narrow path oriented at a 14° angle from the illuminating beam. The intersection of the two beams forms a narrow diamond shaped volume whose major diagonal is under 2 mm in length and is oriented along the optical axis. By means of automated adjustable optics the position of the sampling volume is moved over a distance of 3.5 cm along the optical axis in increments of 0.25 mm. Each such scan takes about 12 seconds. By means of comparison to an internally mounted fluorescence standard which has been calibrated with respect to solutions of known fluorescein concentration, the instrument computes the concentration of fluorescein equivalent to the fluorescence detected in the sampling volume at each scan step. The instrument is also used to determine the fluorescence in the plasma samples by means of an adaptor which holds a cuvette in the scan path.

The mathematical model represents the vitreous as a homogeneous spherical medium enclosed by a thin membrane which is bathed by plasma. The thin membrane models the retinal vessel walls and the pigmented epithelium which are collectively referred to as the blood-retinal barrier (BRB), albeit with an area corresponding to the membrane surface, not the anatomical surfaces. The plasma-vitreous exchange of fluorescein is taken to be a passive process driven by the difference in concentration of free fluorescein adjacent to the two sides of the membrane. However, a flux of fluorescein from vitreous to

blood proportional to the interfacial vitreous concentration is superimposed on the passive exchange because of reports in the literature of a unidirectional retinal fluorescein pump. Transport within the vitreous is currently assumed to be by pure diffusion.

MAJOR FINDINGS: Analysis of measurements on a population of 22 normal volunteers, including six who were measured again on a different day, led to several findings. All of the existing analysis protocols have deficiencies. In general, the sources of random error in the measurements seems to be comparable to variability among normal individuals. Among the consequences of this uncertainty is that the differences between the leakiness parameters of the left and right eyes within individuals were on the average similar to the differences for the same eye among individuals.

SIGNIFICANCE: The shape of the fluorescence profiles and the rate of progressive changes in the profile are indicative of the underlying transport mechanisms for the dye. Changes in the transport mechanisms are expected to occur in pathological conditions. For instance, diabetes, or at least diabetic retinopathy, has been reported to lead to greatly enhanced leakiness of the BRB to fluorescein. Diabetic retinopathy is a major cause of blindness and is a frequent, but delayed sequela in the natural history of diabetes. Various aspects of treatment for retinopathy are experimental. It could be beneficial to have a relatively simple and benign procedure for determining leakiness of the BRB which might be correlated with the progression of the disease, and which is likely to be more sensitive than existing diagnostic procedures, such as visual inspection of the retina. New diagnostic procedures could be used to follow the effectiveness of treatment regimes in slowing the progression of disease or reversing its development. Alternatively, the diagnostic procedure could be used as an early screening tool to determine when to commence treatment.

PROPOSED COURSE: Having made considerable progress in understanding the weaknesses of existing protocols and also the kinetic features of the fluorescein profile development, we are investigating new analysis schemes. It seems clear that a major difficulty which may not have been optimally addressed to date is the influence of the finite sampling volume. Two approaches to dealing with this problem are being examined. One is to deconvolve the instrument output using the measured shaped of the sampling volume before comparison is made between the experimental and model generated profiles. The second approach is to convolve the model mathematically before generating the profiles. After new protocols have been established using the normal volunteer data, we propose examining an established population of diabetic patients.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 RS 10214-01 BEI								
PERIOD COVERED October 1, 1984 to September 30, 1985										
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Photoradiation Therapy										
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) <table style="width: 100%; border: none;"> <tr> <td style="width: 30%;">P.D. Smith, Physicist,</td> <td>BEIB, DRS</td> </tr> <tr> <td>R.F. Bonner Physicist</td> <td>BEIB, DRS</td> </tr> <tr> <td>A. Russo</td> <td>ROB, NCI</td> </tr> <tr> <td>Z. Tochner</td> <td>ROB, NCI</td> </tr> </table>			P.D. Smith, Physicist,	BEIB, DRS	R.F. Bonner Physicist	BEIB, DRS	A. Russo	ROB, NCI	Z. Tochner	ROB, NCI
P.D. Smith, Physicist,	BEIB, DRS									
R.F. Bonner Physicist	BEIB, DRS									
A. Russo	ROB, NCI									
Z. Tochner	ROB, NCI									
COOPERATING UNITS (if any) Radiation Oncology Branch, NCI										
LAB/BRANCH Biomedical Engineering and Instrumentation Branch										
SECTION Electrical and Electronic Engineering										
INSTITUTE AND LOCATION DRS, National Institutes of Health, Bethesda, Md 20205										
TOTAL MAN-YEARS: 1.0	PROFESSIONAL: 1.0	OTHER: 0								
CHECK APPROPRIATE BOX(ES) ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither ☐ (a1) Minors ☐ (a2) Interviews										
SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.) An ascitic murine tumor, embryonal ovarian cell carcinoma, was used as a model of human ovarian carcinoma restricted to the peritoneum. The tumor was treated with a combination of hematoporphyrin derivative and intra peritoneal 514 nm light. Four HPD/laser treatments at 2 day intervals resulted in an 85% cure rate as determined by >100 day survival (untreated mice die between 20 and 23 days following the introduction of the tumor). Toxicity studies of the HPD/laser treatment are being carried out on dogs as a preliminary step for treatment of human patients. The possibility of using singlet oxygen fluorescence as a method of dosimetry is being evaluated.										

OBJECTIVES: To establish the effectiveness of HPD/laser photoradiation therapy as a modality for the treatment of certain cancers.

METHODS EMPLOYED Two to three month old female C₃HeB/FeJ mice were used in this study. A spontaneous embryonal ovarian carcinoma originating in a C₃H mouse is maintained by serial intraperitoneal passages every 3 weeks. This is an ascitic tumor which rarely metastasizes and has tumor deposits on the peritoneal surface which are always less than 3 mm in diameter. 9 days after transplantation, the mice had clinically evident ascites and weighed 2-4 grams more than control mice. By day 25 after transplantation, all untreated mice had died from the tumor; at that time the tumor weighed 20-25 gram. The tumor was transplanted into 68 mice separated randomly on day 9 into two groups. In those mice treated (HPD-Photofrin (50mg/kg body weight) was administered 2 hours prior to irradiation with light. The unanesthetized mouse was placed on its back in an acrylic holder which steadied the abdominal region. A 22 gauge needle punctured the abdominal wall and a 30 gauge stainless steel hypodermic encased 125 optical fiber passed through the needle after which it was withdrawn. The distal tip of the stainless steel hypodermic tubing had a dome of scattering compound suspended in clear epoxy applied; this produced a uniform radiative pattern in all directions from the tip. Typically 10 mW of 514 nm light from an Argon ion laser was passed down the fiber for 2 minutes for each octant of the peritoneal cavity.

50kg dogs were anesthetized and had their peritoneum filled with 3 liters of Ringers in which 0.5% of lippoprotein had been suspended. The Ringers was introduced through an abdominal puncture through which a tracheotomy tube had been passed. This tube also served to introduce the 600 fiber optic light guide through which 4W of 631 nm light (Coherent PRT100 argon pumped dye laser) was directed in 10 minute doses to each octant of the peritoneal cavity. Additional fiber optic probes were used for positioning the 631 nm radiation pattern and for measuring the light dose delivered.

Fluorescent signals of 1.27 were analysed using a lock-in amplifier, and the quadrature component evaluated for increasing the signal relative to the fluorescent background.

MAJOR FINDINGS: All untreated mice transplanted with tumor die within 23 days following implantation of the tumor. Control groups which received either HPD alone or 531 nm light alone showed no increase in survival and died within 23 days. Mice given the HPD/laser treatment all showed improvement (assessed by abdominal girth associated with tumor mass) with a progressive increase in the number of long term survivors corresponding to the number of HPD/laser treatments offered. Four HPD/laser treatments at 2 day intervals starting on day 9 produced an 85% cure with the remaining 15% mortality probably being caused experimentally be seeding of the tumor along the needle tract into the abdominal wall. Mean weight of the mice started at 23 g with the control group increasing to 25 g up to the the 30 days the mice were followed. Implanted mice which received no treatment or HPD and light alone increased in weight steadily until at death they weighed 43 g. Mice given the combined

Z01 RS 10214-01 BEI

HPD/laser treatment had an initial weight loss to 21 g but subsequently gained weight until at day 30 they weighed the same as the control group. HPD uptake studies showed that 2 hours following HPD injection tumor levels range from 5-12 that of other tissues assessed (liver, kidney, muscle, bowel), and remain elevated for 72 hours; both liver and kidney contained substantial levels of HPD.

The toxicity studies in the dogs showed no side effects directly attributable to the HPD/laser treatment. Two dogs died of anesthetic related causes. Irradiation levels of the peritoneal cavity were $20\text{mW}/\text{cm}^2$ in mice treated with HPD.

SIGNIFICANCE: Photoradiation therapy offers an exciting approach for the potential treatment of certain cancers. Ovarian cancer for example kills 11,000 women in the US each year; clearly if the mouse model holds in human subjects PRT will have a significant impact for this disease's morbidity. Singlet oxygen measurement offers the potential of providing dosimetry based on the implicated factor in cell death rather than on the irradiation levels given. Accurate dosimetry is essential to permit widespread use of PRT as an accepted cancer treatment.

PROPOSED COURSE: Completion of the dog toxicity study and extension of the technique to human protocols. To further evaluate the use of singlet oxygen measurement as a method of providing effective dosimetry for photo-therapy.

PUBLICATIONS

Tochner, Z., Mitchell, J., Harrington, F., Smith, P., Russo, D., and Russo, A.: Treatment of murine intraperitoneal ovarian ascitic tumor with hematoporphyrin derivative and laser light. Cancer Res. (in press).

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 RS 10215-01 BEI

PERIOD COVERED

October 1, 1984 to September 30, 1985

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Measurement of Trace-Level Metals and Complexes in Biological Milieux

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

A.F. LeRoy, Ph.D., BEIB; DRS
M. Linnolla, M.D., Ph.D., CPB, NIMH
K. Flora, Ph.D., PRB, NCI
M.K. Wolpert, Ph.D., Drug Eval. Br., DCT, NCI
P. Galle, Prof. of Biophysics, Medical Faculty, Creteil, France
B. Hecquet, Ph.D., Centre Oscar Lambret, Lille France
P. Parsons, Ph.D., BEIB, DRS

COOPERATING UNITS (if any)

CPB-NIMH, DCT-NCI, PRB-NCI, Biophysics Dept., Med. Faculty, Creteil, France;
Centre Anti-cancereux "Oscar Lambret", Lille, France

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Analytical Methods

INSTITUTE AND LOCATION

National Institutes of Health, Bethesda, MD 20205

TOTAL MAN-YEARS:

1.75

PROFESSIONAL:

1.25

OTHER:

0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects☐ (b) Human tissues☐ (c) Neither☐ (a1) Minors☐ (a2) Interviews

SUMMARY OF WORK (Use standard unexpanded type. Do not exceed the space provided.)

Analytical methods have been developed for quantitation and characterization of metallic elements in biological samples. Analysis of vanadium in samples from human subjects under study has been conducted. Results obtained have shown very low values, in the range of nanograms-of-vanadium-per-gram of sample. Such results are obtained only with great difficulty because of the very small amount of sample available. Specific interest in platinum complex behavior of several different compounds used clinically has been studied. Chromatographic techniques are used to make separations of species in solutions. Atomic Absorption spectroscopy with electrothermal atomization(ETA-AAS) is used to quantitate total platinum or single isolated species. HPLC separation with electrochemical detection using a modified polarographic analyzer permits quantitation of the parent CDDP complex in aqueous solutions with a detection limit of about 50 ppb. Analytical methods developed have been used to make kinetic studies of behavior of platinum species from cisplatin in solution.

Z01 RS 10215-01 BEI

OBJECTIVES: To develop and study analytical methods suitable for trace analysis of elements and their compounds and complexes in biological milieux. Emphasis has been on developing techniques for quantitation of elements that have important biological effects such as platinum, vanadium, nickel, cobalt, calcium and iron. More particularly, to conduct the study of the kinetics of transformations of metal-complex compounds used as anti-cancer agents and their transformation products in solution and in the body using improved techniques for identifying, characterizing and quantitating metal complex species in biological samples. Some of these elements are found at trace level concentrations in normal biological tissues but they may also be found at abnormal concentrations in tissues of organisms in some disease states. In still other cases, they may be present as a result of therapeutic intervention.

METHODS EMPLOYED: Ion exchange chromatography has been used successfully as a method to resolve metal-ion complexes in in vitro studies. In vivo studies with patients being treated with cis-platin (cis-diamminedichloroplatinum (II), (CDDP) formulated for clinical use) have involved quantitative analysis and characterization of the metal-complex species in urine. The technique has been applied to studies of the reaction in vitro to establish quantitative rate data describing the transformations. It was recognized from our early work that CDDP formulated as cisplatin with mannitol and NaCl (and HCl to adjust pH) is transformed in solution into charged and uncharged species. The present work was undertaken to make quantitative measures under differing conditions to measure the influence of [Cl] on the rate and extent of hydrolysis and to establish the feasibility of material balance studies for the various species and obtain the several species in sufficient quantity and purity to permit characterization. In addition, HPLC techniques have been studied to establish their performance and characteristics. Detection using electrochemical methods has been adapted to supply a rapid, on-line technique with good sensitivity.

In vitro studies with human tumors cultured in defined medium have been undertaken with Cisplatin, CBDCA, and TNO-6 to establish the uptake characteristics of these complexes under conditions simulating the therapeutic conditions of chemo-embolization.

MAJOR FINDINGS: Ion exchange separations of platinum species in aqueous media can be made quantitative with respect to each of the species separated and provide excellent data for kinetic studies. Together with other data for the behavior in solution, they are providing the basis for a systematic study of this complex system which should furnish the data for better understanding of the mechanism by which the platinum drugs work.

An evaluation of current analytical techniques has shown that High Performance Liquid Chromatography (HPLC) coupled with Electrochemical Detection (EC) can be used to separate cis-diamminedichloroplatinum (II) (CDDP) from its hydrolysis products and detect it at levels down to 50 ppb. Separation of the

platinum species, of which some are cationic complexes, is readily achieved by Paired Ion Chromatography (PIC). A number of paired ion reagents were evaluated and PIC B7 (Heptane sulfonic acid) was found to give the best separation on a C18 Reverse Phase column. The optimum mobile phase with PIC B7 was 10mM sodium acetate at pH 4.60. A comparison of electrochemical detector systems was carried out and it was found that a modified Polarographic Analyzer with a Hanging Mercury Dropping Electrode (HMDE) gave the best results. Chromatograms of aged drug solutions show several peaks some of which have been identified as platinum-containing using ETA-AAS. The method was used to study the binding of CDDP to human plasma in vitro. It was shown that the parent drug can be determined in plasma ultrafiltrate. After 2 days incubation with 10ug/ml CDDP, the parent drug was not detected in plasma ultrafiltrate.

PROPOSED COURSE: The principal work on method development and reaction kinetics has been with CDDP, thus far. Further studies with CDDP in vitro and in vivo are planned together with studies of some of the second generation platinum drugs in clinical use or in toxicologic evaluation studies. Preliminary experiments suggest the applicability of the analytical techniques already developed is generally valid with minor modifications required in some cases. In the case of EC detection with chromatographic methods of separation, the response of the electrochemical detector is highly dependent on the stereochemistry of the complex. Thus further refinement may be possible using post-column derivitization prior to the EC detection.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 RS 10216-01 BEI

PERIOD COVERED

October 1, 1984 to September 30, 1985

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Enzyme Purification - Calmodulin

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

A.F. LeRoy Ph.D., BEIB/DRS

R. Berger, Ph.D., LTD, NHLBI

COOPERATING UNITS (if any)

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Analytical Methods

INSTITUTE AND LOCATION

DRS, National Institutes of Health, Bethesda, MD 20205

TOTAL MAN-YEARS:

0.2

PROFESSIONAL:

0.1

OTHER:

0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects☐ (b) Human tissues☐ (c) Neither☐ (a1) Minors☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Validity of studies characterizing and measuring properties of calmodulin depend on having quantifiable measures of purity of the enzyme preparation and the proportion of calcium it contains and requires the availability of extremely pure reagents, buffer, and solvents and contamination free labware.

Analytical methods have been developed for quantitation of picogram quantities of calcium in highly purified preparations of calmodulin and in the reagents and solvents needed to make the preparations. Preliminary analyses show that the needed reagents and solvents for making ultra-pure enzyme preparations can be freed to satisfactory levels from such ubiquitous contaminants as calcium using techniques developed in our laboratory.

Z01 RS 10216-01 BEI

OBJECTIVES: Develop techniques for quantitation of calcium at picogram levels in samples containing microgram quantities of enzyme and develop supply of reagents and solvents necessary for making enzyme preparations of the desired purity in the quantity needed for NIH studies.

MAJOR FINDINGS: Analytical Methods have been developed for quantitation of picogram quantities of calcium in highly purified preparations containing microgram quantities of calmodulin. Validity of method has been confirmed through analysis of appropriate NBS Standard Reference Materials. Preliminary analyses show that the needed reagents, buffers, and solvents can be freed from such common contaminants as calcium using techniques developed in our laboratory to concentration levels that are satisfactory and can be made in the necessary quantity for present laboratory needs.

PROPOSED COURSE: Develop larger scale system for production of purified reagents, buffers, and solvents in the quantities needed as related research project activity increases need. Develop suitable facilities as anti-contamination requirements become more stringent.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 RS 10217-01 BEI
PERIOD COVERED October 1, 1984 to September 30, 1985		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Compact, Time-Domain Displays of Speech Signals		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) H.S. Eden, M.D., Ph.D., Deputy Chief, BEIB, DRS M. Eden, Ph.D., Chief, BEIB, DRS M.H. Goldstein, Ph.D., The Johns Hopkins University J.M. Heinz, Ph.D., The Johns Hopkins University		
COOPERATING UNITS (if any) Department of Electrical Engineering and Instrumentation Branch		
LAB/BRANCH Biomedical Engineering and Instrumentation		
SECTION Office of the Chief		
INSTITUTE AND LOCATION DRS, National Institutes of Health, Bethesda, MD 20205		
TOTAL MAN-YEARS: .5	PROFESSIONAL: .5	OTHER: 0
CHECK APPROPRIATE BOX(ES) ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither ☐ (a1) Minors ☐ (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) The objective of this work was to develop a display of speech signals that provides useful, visually extractable information supplementary to that apparent in spectrograms. The approach was to develop and analyze pitch-synchronous displays of the acoustic pressure wave in which successive pitch intervals of voiced speech are time-aligned and closely spaced. Methods were developed for automated and semi-automated epoch extraction, based upon the nearest-neighbor algorithm and extrapolations from pitch-period contours. Theoretical studies relevant to such displays included the effects of the fundamental frequency of vocal fold oscillation on the time waveform, the effects of locally zeroing the spectral phase of time signals, and the mathematical relationship existing between spectrograms and pitch-synchronous time-domain displays. Through a known generalization of Shannon's sampling theorem, it was shown that the line spectrum of voiced speech is generally an undersampled version of the spectral envelope associated with a given vocal tract configuration; using a theorem by Linden and Abramson, conjectures were developed on ways that listeners might use the "jitter" normally found in speech to compensate for such undersampling and to aid constancy in perception of a vowel's identity as it is heard at different pitches.		

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 HS 10218-01 BEI

PERIOD COVERED

October 1, 1984 to September 30, 1985

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Composition of Chromaffin Secretory Granules by Analytical Electron Microscopy

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

R.D. Leapman Visiting Scientist BEIB, DRS

Others:

R.L. Ornberg Biophysicist LCBG, NIADOK
C.E. Flori Physical Scientist BEIB, DRS

COOPERATING UNITS (if any)

Computer Systems Laboratory, Division of Computer Research and Technology, NIH
(K.E. Gorlen)

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Electron Beam Imaging and Microspectroscopy Group

INSTITUTE AND LOCATION

DRS, National Institutes of Health, Bethesda, MD 20205

TOTAL MAN-YEARS:

0.5

PROFESSIONAL:

0.5

OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects☐ (a1) Minors☐ (a2) Interviews☐ (b) Human tissues☐ (c) Neither

SUMMARY OF WORK (Use standard unredacted type. Do not exceed the space provided.)

The elemental composition of the secretory granules of bovine adrenal chromaffin cells has been determined by a combination of electron energy loss spectroscopy and energy dispersive x-ray spectroscopy. Ultrathin cryosections of rapidly frozen cultured cells were prepared and transferred at -170°C into the Hitachi H700H analytical electron microscope using a Gatan cryotransfer sample stage. Specimens were dehydrated in situ by warming up to -100°C and spectra were recorded at this temperature to help minimize mass loss due to radiation damage. Energy loss spectra were recorded in an attempt to determine the nitrogen-to-phosphorus ratio and hence to estimate the relative amounts of nucleotides, proteins and catecholamines in the granules. Energy dispersive spectra recorded at known dose were used to determine concentrations of potassium, calcium, chlorine, sodium and phosphorus. The results could be compared with existing data from isolated granules.

Z01 RS 10218-01 BEI

OBJECTIVES: To determine the chemical composition of adrenal chromaffin granules in rapidly frozen cells both in terms of the organic components, i.e., proteins, nucleotides or catecholamines and the diffusible ions, i.e., potassium, sodium, chlorine and calcium.

METHODS EMPLOYED: Ultrathin cryosections of rapidly frozen chromaffin cells were transferred at low temperature into the Hitachi H700H analytical electron microscope. X-ray spectra were recorded using a Tracor Northern side-looking energy dispersive x-ray detector, and energy loss spectra were recorded with a Hitachi and subsequently a Gatan 607 magnetic sector spectrometer. The spectra were analyzed with the PDP 11/60 computer by means of quantitative programs developed in BEIB. A large population of granules were analyzed in addition to other components such as the mitochondria, nuclei, cytoplasm and extracellular matrix.

MAJOR FINDINGS: The concentration of calcium in the granule was estimated as 12 mmol/kg wet weight. The potassium concentration was ca 40 mmol/kg compared with 130 mmol/kg in the cytoplasm. Rather surprisingly the chlorine concentration of ca 13 mmol/kg in the granule was only slightly greater than in the cytoplasm (ca. 10 mmol/Kg). This result may be explained by the relatively smaller water content of the granule. The ratio of protein to nucleotide in the granule (ca. 2:1) estimated from the nitrogen-to-phosphorus ratio was consistent with data from isolated granules.

SIGNIFICANCE: The determination of diffusible ion concentrations and the amounts of organic components in rapidly frozen cells could be helpful in understanding the changes that take place in exocytosis. Measurements on isolated granules are not always reliable and analytical electron microscopy in intact-cells offers a useful alternative approach.

PROPOSED COURSE: It is planned to try to determine the amount of catecholamines in the secretory granules by obtaining N:S and N:P ratios which give the fraction of nitrogen in the protein and nucleotide components respectively. Elemental compositions will also be obtained for cells that have been stimulated for example by treatment with reserpine.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 RS 10219-01 BEI

PERIOD COVERED

October 1, 1984 to September 30, 1985

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Quantitative Elemental Mapping of Rapidly-frozen Neural Tissue

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

R. D. Leapman

Visiting Scientist

BEIB

Others:

S.B. Andrews

Special Expert

LN, NINCDS

T.S. Reese

Chief

LN, NINCDS

C.E. Fiori

Physical Scientist

BEIB, DRS

C.R. Swyt

Physical Scientist

BEIB, DRS

COOPERATING UNITS (if any)

Computer Systems Laboratory, Division of Computer Research and Technology, NIH
(K. Gorlen)

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Electron Beam Imaging and Microspectroscopy Group

INSTITUTE AND LOCATION

DRS, National Institutes of Health, Bethesda, MD 20205

TOTAL MAN-YEARS:

0.5

PROFESSIONAL:

0.5

OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects☐ (b) Human tissues☐ (c) Neither☐ (a1) Minors☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Elemental Maps showing the distributions of calcium, potassium and sodium have been obtained from freeze-dried ultrathin cryosections of rapidly-frozen mouse cerebellar cortex. The molecular layer of the cerebellum was imaged by emission of characteristic x-rays with the use of an energy dispersive spectrometer on the BEIB analytical electron microscope. Data were obtained from resting or from repetitively stimulated tissue in order to investigate changes in ion distribution that occur on excitation. There was particular interest in determining the location of calcium concentrations that may be involved as intracellular stores required for transmission of nerve impulses. It was necessary to establish practical limits for calcium detection in an elemental map. Since the image is obtained serially, sensitivity depends on the number of pixels, i.e. on the image resolution. In practice, concentrations of about 10-20 mmol/kg wet weight could be detected.

Z01 RS 10219-01 BEI

OBJECTIVES: To obtain elemental distributions in dried ultrathin cryosections of mouse cerebellar cortex and to relate these distributions to the morphology of the tissue.

METHODS EMPLOYED: Rapidly frozen ultrathin cryosections were studied in a Hitachi H700H analytical electron microscope controlled by a Digital Equipment Corporation PDP 11/60 computer and LSI 11/23 satellite processor. X-ray maps were obtained from freeze-dried samples by means of a side-looking Tracor Northern energy dispersive x-ray detector. The resulting data were analyzed quantitatively using a DeAnza IP 6400 image display system and software developed in collaboration with CSL, DCRT.

MAJOR FINDINGS: Pre-synaptic calcium stores were not evident in the glutaminergic parallel fiber/Purkinje cell synapses of resting or stimulated cerebellar cortex. However, repetitively stimulated tissue contained focal concentrations of calcium (< 200 nm in diameter) containing ca. 35 mmol/kg wet weight, which may correspond to cisternae of endoplasmic reticulum in the spines of the Purkinje cell dendrites. Some higher concentrations of calcium seen in the cell mitochondria could be due to tissue damage.

SIGNIFICANCE: The results suggest a fundamental difference between pre-synaptic and post-synaptic nerve endings regarding mechanisms of calcium mobilization and transport. It is possible that the concentrations of calcium in the postsynaptic Purkinje cell spines are internal storage or buffering organelles which are involved in regulating calcium ions during excitation.

PROPOSED COURSE: It will be necessary to improve the techniques for correlating the elemental distributions with tissue morphology. It is hoped to improve conditions for cryosectioning to reduce sectioning artifacts and increase contrast in the STEM images. It is also planned to obtain data from tissue incubated in strontium rather than calcium in an effort to understand if the organelles in the spines are used to buffer extracellular calcium or if they function as internal stores.

PUBLICATIONS

Andrews, S.B., Leapman, R.D., Landis, D.M.D., Fiori, C.E., and Reese, T.S.: Elemental distribution in rapid-frozen cerebellar cortex. J. Cell Biol. 99: 424a, 1984.

Andrews, S.B., Leapman, R.D., Landis, D.M.D., Fiori, C.E., and Reese, T.S.: Rapid freezing and quantitative elemental imaging in neurobiology. In Bance, G.N. (Ed.): Proc. 12th Annual Meeting of the Microscopical Society of Canada, Microscopical Society of Canada, 1985, pp. 24-24.

Andrews, S.B., Leapman, R.D., Landis, D.M.D., Fiori, C.E. and Reese, T.S.: Quantitative elemental imaging of rapidly frozen neural tissues: applications to the identification of intracellular calcium stores. In Proc. Low Temperature Biological Microscopy Meeting, Royal Microscopical Society of Great Britain, 1985 (in press).

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 RS 10220-01 BEI

120

PERIOD COVERED

October 1, 1984 to September 30, 1985

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Elemental Imaging of Alzheimer's Disease Related Brain Tissue

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

C.E. Fiori, Physical Scientist, BEIB, DRS

David Nochlin, Senior Staff Fellow, LN, NIA

C.R. Swyt, Physical Scientist, BEIB, DRS

COOPERATING UNITS (if any)

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Electron Beam Imaging and Microspectroscopy Group

INSTITUTE AND LOCATION

DRS, National Institutes of Health, Bethesda, MD 20205

TOTAL MAN-YEARS:

0.5

PROFESSIONAL:

0.5

OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects

☐ (b) Human tissues

☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Images of the distributions of calcium and aluminum in various brain tissues are being acquired by wavelength dispersive x-ray spectrometry in a Cameca MBX microprobe. The tissues are obtained by autopsy from patients exhibiting the clinical and pathological symptoms of Alzheimer's Disease and matched controls, and from rats fed an aluminum-rich diet and controls.

Z01 RS 10220-01 BEI

OBJECTIVES: Comparison of distributions of Ca and Al within cells and among cells in tissues from various regions of brain of subjects and controls by analysis of elemental x-ray images.

METHODS EMPLOYED: 20 micron thick cryosections of fresh frozen tissue are mounted on spectroscopically pure carbon substrates. Under computer control, the electron beam of the Cameca MBX microprobe is stepped over the area to be imaged in an orderly array of acquisition points. The secondary electron (SE) or, simultaneously, the backscattered electron (BSE) and two wavelength dispersive (WDS) characteristic x-ray signals are collected for a selected time at each point. The data stored in arrays in computer memory are displayed as digital images. The images reveal morphology (SE), atomic number contrast (BSE), or elemental distribution (WDS). The WDS images can be quantitated by use of standards to determine elemental concentrations in any feature. The acquisition software for the PDP 11/60 computer was written by members of CSL/DCRT.

MAJOR FINDINGS: Preliminary data does not yet permit any conclusions concerning the role of Ca or Al in the disease process.

SIGNIFICANCE: Aluminum has been reported to occur in relatively high concentrations in the neurofibrillary tangles associated with a number of central nervous system diseases in humans. In rats fed an Al - rich diet, increased concentrations of Al have been observed in whole brain and gray matter. It is hoped that the distributions of Ca and Al in the elemental images of the various tissues, and the cells within them, here under study will elucidate the role of these elements in the pathogenesis of such diseases as AD.

PROPOSED COURSE: Acquisition and analysis of images will proceed as described.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 RS 10221-01 BEI
PERIOD COVERED October 1, 1984 to September 30, 1985		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Elemental Imaging of Alveolar Macrophages		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) C.R. Swyt, Physical Scientist BEIB, DRS C.E. Flori, Physical Scientist, BEIB, DRS R.D. Leapman, Visiting Scientist, BEIB, DRS W. Rom, Senior Fellow, PB, NHLBI		
COOPERATING UNITS (if any)		
LAB/BRANCH Biomedical Engineering and Instrumentation		
SECTION Electron Beam Imaging and Microspectroscopy Group		
INSTITUTE AND LOCATION DRS, National Institutes of Health, Bethesda, MD 20205		
TOTAL MAN-YEARS: 0.5	PROFESSIONAL: 0.5	OTHER:
CHECK APPROPRIATE BOX(ES) ☐ (a) Human subjects ☐ (a1) Minors ☐ (a2) Interviews ☐ (b) Human tissues ☐ (c) Neither		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) Refractile particles are observed by light microscopy (LM) in alveolar lavaged macrophages from patients exhibiting clinical symptoms of asbestosis, silicosis and coal-miner's emphysema. However the elemental composition and location of these particles in the ultrastructure of the macrophages cannot be determined by LM. Elemental x-ray images obtained in the CAMECA MBX microprobe from large fields of whole air-dried macrophages have enabled investigators to correlate particle composition with disease. High resolution images of individual macrophages in ultrathin sections of epon embedded preparations obtained in the Hitachi H700H analytical electron microscope utilizing bright field (BF), energy dispersive x-ray (EDS) and electron energy loss (EELS) signals have revealed both elemental composition and ultrastructural location of the particles.		

Z01 RS 10221-01 BEI

OBJECTIVES: The objectives of the collaboration were to determine the composition of refractile particles observed by light microscopy in the alveolar lavaged macrophages of patients exhibiting clinical symptoms of asbestosis, silicosis, and coal-miner's emphysema, and to correlate element with clinical condition and ultrastructure.

METHODS EMPLOYED: Aliquots of the order of 1 ml of H₂O washed fixed cell suspensions were dispersed by aerosol spray onto spectroscopically pure carbon substrates. Not less than 50 cells of each preparation were imaged in the CAMECA MBX microprobe using the secondary electron signal and the wavelength dispersive x-ray signals from two selected elements simultaneously. The elements tabulated in this study were Ca, Si, Mg and Fe. Preparations of cells from both normal volunteer controls and clinically diagnosed patients were imaged.

Ultra-thin sections of conventionally prepared epon embedded suspensions were imaged in the Hitachi H700H analytical electron microscope using signals from a Tracor Northern side looking energy dispersive x-ray detector, a magnetic sector EELS spectrometer and a conventional bright field detector. Images of the distribution of C, Fe, Si, and Mg were produced using the EELS and EDS signals.

The x-ray signals from selected elements were acquired concurrently. All data were acquired under control of imaging software written by CSL/DCRT and running on the PDP 11/60 computer.

SIGNIFICANCE: Elemental analysis of particulates observed in alveolar lavaged macrophages could reduce ambiguity of cause of pulmonary disease diagnosed from clinical symptoms.

PROPOSED COURSE: Analysis of data will be completed. Images of biopsied alveolar tissue will be acquired in the analytical microscope to determine distribution of particles in the lung tissue itself.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 RS 10222-01 BEI

PERIOD COVERED

October 1, 1984 to September 30, 1985

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Elemental Distributions in Central Nervous System Tissues

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

C.R. Swyt Physical Scientist BEIB/DRS
R.M. Garruto Senior Biologist CNSS/NINCDS
C.E. Fiori Physical Scientist BEIB/DRS

COOPERATING UNITS (if any)

CNSS/NINCDS

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Electron Beam Imaging and Microspectroscopy Group

INSTITUTE AND LOCATION

DRS, National Institutes of Health, Bethesda, MD 20205

TOTAL MAN-YEARS:

.5

PROFESSIONAL:

.5

OTHER:

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The occurrence of neurofibrillary tangles and plaques is common to a number of central nervous system disorders including Guamanian amyotrophic lateral sclerosis (ALS), parkinsonism with dementia (PD), and Alzheimer's disease. These NFTs and plaques contain nonessential metals and elevated levels of biological elements. Fixed and frozen thick sections of hippocampus and frontal cortex of human brain from subjects exhibiting symptoms of these diseases have been examined in the CAMECA MBX microprobe. Wave length dispersive x-ray spectrometry (WDS) performed at selected areas has provided both spectra and digital images showing the distribution of elements of interest in the specimens.

Z01 RS 10222-01 BEI

OBJECTIVES: The objective of this collaboration is to obtain both x-ray spectra and digital x-ray images of the distribution of calcium, aluminum and other implicated elements in sections of brain from control cases and cases showing pathological symptoms of these central nervous system diseases, and to establish correlation of elevated concentrations with morphology from the gross to ultrastructural levels.

METHODS EMPLOYED: 20 micron thick sections of fixed and frozen sections of hippocampus and frontal cortex are cut and mounted on spectroscopically pure carbon substrates. The pathology of the specimen has been characterized by light microscopy (LM), frequently on adjacent sections. Sections are examined in the secondary electron imaging mode (SEI) of the CAMECA MBX microprobe and the areas to be imaged are selected by characteristic morphology. Under computer control, the SEI signal and, simultaneously, the back-scattered electron signal (BSE) and two characteristic x-ray WDS signals are collected from a regular array of up to 512x512 analysis points in a field of up to 1mmx1mm. These arrays of data are displayed as digital images. The characteristic x-ray images reveal the distribution of the two elements selected and can be quantified. The SEI and BSE images provide correlation of elemental deposition with the characteristic morphology.

MAJOR FINDINGS: Inteneuronal accumulations of calcium and aluminum have been confirmed in Guamian ALS, PD and Alzheimer's disease specimens.

PROPOSED COURSE: Work will continue of the disease specimens mentioned by the methods described. Specimens for analysis will also be provided from subjects with other central nervous system disorders such as Down'd syndrome, Creutzfeldt-Jakob disease and kuru. Higher resolution work will be pursued on the Cameca microprobe, and analysis of ultrathin embedded and cryo-sections and isolated neurofilaments will be performed on the Hitachi H700H analytical electron microscope.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 RS 10223-01 HEI
PERIOD COVERED August 1, 1984 to August 1, 1985		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Individual Human Peripheral Mononuclear Cell Magnesium Quantitation		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) G.R. Hook, Staff Fellow, Biomedical Engineering and Instrumentation Branch, DRS R.J. Elin M.D., Ph.D., Chief, Clinical Pathology Department, Clinical Center		
COOPERATING UNITS (if any) Clinical Pathology Department, Clinical Center		
LAB/BRANCH Biomedical Engineering and Instrumentation		
SECTION Electron Beam Imaging and Microspectroscopy Group		
INSTITUTE AND LOCATION DRS, National Institutes of Health, Bethesda, MD 20205		
TOTAL MAN-YEARS: 1	PROFESSIONAL: 1	OTHER:
CHECK APPROPRIATE BOX(ES) ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither ☐ (a1) Minors ☐ (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) Total body magnesium (Mg) is inversely correlated with heart disease, atherosclerosis and hypertension. Serum Mg is a poor indicator of total body Mg but peripheral blood mononuclear cell Mg may be a good indicator. Peripheral blood mononuclear cells are a heterogeneous population of lymphocytes and monocytes, with monocytes being twice the volume of lymphocytes. To evaluate mononuclear cell Mg, the mean cell Mg of the population, the individual cell Mg distribution within the population and the relationships between cell Mg and cell size must be determined. Whereas atomic absorption spectroscopy (AAS) methods have been developed to measure the mean mononuclear cell Mg, methods for measuring the Mg of individual mononuclear cells have not been described. We have developed a method for the quantification of Mg in individual whole mononuclear cells by electron probe X-ray microanalysis (EPMA). Whole blood is anticoagulated with heparin, washed with buffered saline glucose and ultracentrifuged in a discontinuous stractan density gradient. Isolated mononuclear cells are washed with isoosmotic, pH neutral ammonium nitrate, spray deposited on thin film supports, air dried and carbon coated for EPMA. The Mg concentration is determined by the peak-to-local continuum X-ray intensity ratio. Glass microsphere standards obtained from the National Bureau of Standards were used to calibrate the analysis. The mean cell Mg concentrations determined by AAS and EPMA were not significantly different. The coefficient of variation for replicate analysis of the standard by EPMA was 10%. The net variation in Mg concentration among individual cells was 20% and the distribution was symmetrical. The Mg concentration was independent of cell size but the cell Mg content (fg/cell) increased with cell size.		

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 RS 10224-01 BEI

PERIOD COVERED

October 1, 1984 to September 30, 1985

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Modified Fourier Transform Techniques

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

Michael Unser, Visiting Fellow, BEIB/DRS

COOPERATING UNITS (if any)

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Office of the Chief

INSTITUTE AND LOCATION

DRS, National Institutes of Health, Bethesda, MD 20205

TOTAL MAN-YEARS:

PROFESSIONAL

OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects☐ (b) Human tissues☐ (c) Neither☐ (a1) Minors☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The Discrete Fourier Transform is widely used in signal processing for the computation of correlation or convolution equations. The aim of this project has been to study some alternatives that may be more suited for the processing of real signals. The definition of a class of transforms with pseudo-cyclic convolution properties has led to the discovery of a modified Fourier transform that allows efficient computation of aperiodic convolutions. In contrast to conventional Fourier transform techniques, this method does not require zero padding to suppress wraparound or aliasing errors. It requires less memory and less computation time than conventional complex algorithms.

Z01 RS 10224-01 BEI

OBJECTIVES: The objectives of this project are the theoretical study of selected general purpose algorithms or methods for signal processing and their application in the context of biomedical engineering.

METHODS EMPLOYED: The studies methods have been simulated and evaluated using computers. The symbolic algebra manipulation program REDUCE, available on the DEC-10, has also been used in order to verify some calculations.

MAJOR FINDINGS: The real convolution algorithm based on the modified Fourier transform provides a gain of a factor of two, in both storage and time, over the usual complex algorithm. Furthermore, it is easily implemented using FFT's (Fast Fourier Transform) of the same size as the signals to be processed. This method has been applied to the alignment, based on cross-correlation calculation, of one-dimensional signals obtained from high resolution micrographs. The corresponding program has been included in CSL/DCRT's image processing software package (PIC).

SIGNIFICANCE: Digital filtering techniques are commonly used in biomedical engineering applications. The use of efficient computational methods allows a saving in both time and storage.

PUBLICATIONS:

Unser, M.: A modified fourier transform for aperiodic convolution. (submitted for publication)

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 RS 10225-01 BEI

PERIOD COVERED

October 1, 1984 to September 30, 1985

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Processing of High Resolution Electron Micrographs

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

Michael Unser, Visiting Fellow, BEIB/DRS
Thierry Pun, Visiting Fellow, BEIB/DRS
Benes Trus, Research Chemist, CSL/DCRT
Alasdair C. Steven, Visiting Scientist, LPB/NIADDK

COOPERATING UNITS (if any)

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

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INSTITUTE AND LOCATION

DRS, National Institutes of Health, Bethesda, MD 20205

TOTAL MAN-YEARS:

PROFESSIONAL:

OTHER:

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects
☐ (a1) Minors
☐ (a2) Interviews

☐ (b) Human tissues☐ (c) Neither

SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.)

High resolution micrographs are often of poor quality, due to various distortions and especially to a very low signal-to-noise ratio. Visual quality can be improved significantly by appropriately combining several observations of similar subjects. The aim of this project is to develop signal processing techniques to facilitate structure determination from such electron micrographs. Methods for translational and rotational alignment of different views of the same subject have been developed and implemented. Principal components and correspondence analysis have been used to seek important characteristics of the data. A procedure for automated statistical rejection of outlying samples has been proposed. These methods have been applied successfully to the structure determination of Herpes and T7 viruses by combining as many as 50 different observations of the same object.

Z01 RS 10225-01 BEI

OBJECTIVES There are currently four main objectives in this research: (1) The determination of appropriate statistical models (noise and various distortions) for high resolution micrographs, (2) the study of algorithms for the alignment of samples, (3) the decision procedure which concerns the classification of different views as well as the detection of "bad" samples, (4) the assessment of the quality of the result obtained by averaging (signal-to-noise improvement, resolution).

METHODS EMPLOYED: Several programs have been developed in FORTRAN 77 on CSL's image processing facility (VAX 780). The alignment (translation rotation) of the subjects is performed iteratively and is based on computation of the cross-correlation function with respect to a reference image. Principal component analysis (Karhunen-Loeve transform) is used for data compression and statistical interpretation. The automated detection of "bad" subjects is performed iteratively to reject the less likely samples (with respect to some statistical model) or equivalently to maximize the likelihood of the remaining samples.

MAJOR FINDINGS: The implemented algorithms were found to perform well and allowed an important reduction of the signal-to-noise ratio - corresponding to an important improvement of the image quality - when applied to Herpes and T7 viruses. The statistical procedure for detection of abnormal samples produced very satisfying results, in the sense that its selection matched almost perfectly with human "subjective" judgement.

SIGNIFICANCE: The acquired scientific expertise and the developed software should allow other scientists, primarily at NIH, to use these image processing and computer reconstruction techniques to determine or understand a specimen's structure. Furthermore, the use of statistical methods provides quantitative results and facilitates decision making.

PROPOSED COURSE: A careful study of the underlying statistical processes (noise modeling), the automated classification of observations that may for example correspond to different angular projections of the same specimen and the assessment of spatial resolution are among aspects that still have to be considered. We are also planning to apply reconstruction techniques from projected data for three dimensional structure determination.

